PEGGY PENCE, PhD, RAC, FRAPS
EXPERT WITNESS REPORT

RE: TENSION FREE VAGINAL TAPE (TVT) SYSTEM
PRODUCT LIABILITY LITIGATION
vs. ETHICON, INC.
AND JOHNSON & JOHNSON
(Collectively referred to in this Report as Ethicon)

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List of Key Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
AHWP	Asian Harmonization Working Party
BLA	Biologics License Application
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CRO	Clinical Research Organization
CSUCI	California State University Channel Islands
CSUPERB	California State University Program for Education and Research in Biotechnology
CT	Cytotoxicity
DHCP	Dear Health Care Professional
DDUPSA	Division of Device User Programs and Systems Analysis
DFU	Directions for Use
DIA	Drug Information Association
DIS	Detrusor Instability Score
DSC	Differential Scanning Calorimetry
EWHU	Ethicon Women's Health and Urology
FAERS	FDA Adverse Event Reporting System (formerly AERS)
FDA	U.S. Food and Drug Administration
FDAMA	FDA Modernization Act of 1997
FDCA/FD&C Act	Federal Food, Drug, and Cosmetic Act
FRAPS	Regulatory Affairs Professionals Society Fellow
FTC	Federal Trade Commission
GAO	Government Accountability Office
GBP	British Pound
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HHS	Department of Health and Human Services
ICDs	Implantable Cardioverter Defibrillators
IDE	Investigational Device Exemption
IEC	International Electrotechnical Commission
IFU	Instructions for Use
IIQ-7	Incontinence Impact Questionnaire-Short Form
IL	Interleukin
IMDRF	International Medical Device Regulators Forum
IMT	Inflammatory Myofibroblastic Tumor
Inc.	Incorporated
ISO	International Organization for Standardization
IV	Intravenous
J&J	Johnson & Johnson Company
KOL	Key Opinion Leader
LCM	Laser Cut Mesh
LC	Laser Cut
LLC	Limited Liability Company
MAUDE	Manufacturer and User Facility Device Experience Database

MCM	Mechanical Cut Mesh
MDA	Medical Device Amendments
MDR	Medical Device Reporting
MedDRA	Medical Dictionary for Regulatory Activities
MS	Master of Science
NCA	National Competent Authority
NDA	New Drug Application
NHDS	National Hospital Discharge Survey
NSE	Not Substantially Equivalent
OCRA	Orange County Regulatory Affairs Discussion Group
ODE	Office of Device Evaluation
OTC	Over-the-Counter
PDP	Polyethylene
PET	Polyethylene Terephthalate
PhD	Doctor of Philosophy
PHN	Public Health Notification
PG	Polyglactin
PMA	Premarket Approval Application
POP	Pelvic Organ Prolapse
PP	Polypropylene
PTFE	Polytetrafluorethylene
PVS	Pubovaginal Sling
QOL	Quality of Life
QSR	Quality System Regulation
RAC	Regulatory Affairs Certification
RAPS	Regulatory Affairs Professionals Society
RCT	Randomized, Controlled Clinical Trials
SCC	Squamous Cell Carcinoma
SE	Substantially Equivalent
SEM	Scanning Electron Microscopy
SG2	GHTF Study Group 2
SMDA	Safe Medical Devices Act of 1990
SPARC	Supra Pubic Arc
SUI	Stress Urinary Incontinence
S.W.O.T.	Strengths, Weaknesses, Opportunities, Threats
TGA	Thermogravimetric Analysis
TOT	Transobturator Tape
TVT	Tension-free Vaginal Tape
TVT-O	Tension-free Vaginal Tape Obturator
UC	Ultrasound Cut
UDI	Urogenital Distress Inventory
UI	Urinary Incontinence
US or U.S.	United States of America
U.S.C.	United States Code
UTI	Urinary Tract Infection
VOC	Voice of Customer
WCQ	Worldwide Customer Quality

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I. CREDENTIALS AND METHODOLOGY

A. Credentials: Qualifications and Experience

I have more than 40 years of experience in the research and development of traditional pharmaceuticals, biotechnology-derived therapeutics (biopharmaceuticals), and medical devices, including in vitro diagnostics. I began my career at Eli Lilly and Company in 1970 in basic immunology research and later transitioned to clinical and regulatory affairs. I subsequently held project management and clinical management positions, from 1983 to 1992, at a number of emerging-growth companies, including Serono Laboratories (U.S. start-up), Triton Biosciences (acquired by Berlex Laboratories, Inc.), and Amgen, Inc.

In 1992, I founded a consulting firm that was incorporated in 1995 as Symbion Research International, Inc., a full-service contract research organization (CRO) and consulting firm. I have been President and Chief Executive Officer since that time. In this position, I provide advice, guidance, and product development services to pharmaceutical/biopharmaceutical and medical device companies in the areas of strategic planning, preclinical testing, clinical trials design and conduct, and regulatory matters involving the U.S. Food and Drug Administration (FDA), as further discussed below. In January 2012, I co-founded Illuminostics, LLC, to provide medical imaging services for clinical trials and to aid in the diagnosis and monitoring of disease in medical practice.

Over the course of my career, I have worked with more than 80 companies and over 90 medical devices, pharmaceuticals (drugs), and biopharmaceuticals (biologic therapeutics), including combination products (e.g., device-drug combination products). I have guided and coordinated product development activities from manufacturing process development through marketing plans and have led development programs for a number of novel therapeutics and medical devices. My medical device experience encompasses all Classes of medical devices: Classes I, II and III. I have broad experience spanning multiple therapeutic areas, including women's health, neurology, neuropsychology, oncology, hematology, infectious disease, rheumatology, nephrology, respiratory disorders, metabolic and growth disorders, gastroenterology, burns, wound healing, and ophthalmology. As regards women's health and wound healing and of particular relevance to the subject matter of this Report, I have designed clinical trials for diseases of the female genital system and have been involved in both preclinical and/or clinical testing of novel medical devices and biologics for wound healing applications, including both deep wounds and surgical incisions.

Notably, the product materials I have reviewed for this Report are the same types of materials I have either prepared or reviewed to assure their accuracy, completeness, and regulatory compliance during the course of my professional career. Further, Ethicon's responsibilities about which I have opined are the same types of responsibilities I have executed over the course of my career in medical product development. I have been an integral or leading member of multiple product development teams to determine the testing requirements for medical devices and drugs/biologics and to make decisions concerning whether additional testing and, if so, what types of additional testing were needed based on initial results of product testing. I have advised manufacturers on the adequacy of proposed medical device labeling. I have also contributed substantially to the development and content of product labeling, including for medical devices. For example, I have prepared clinical study reports and summarized key findings, including safety information, for inclusion in labeling. Further, I have written a number of Investigator's Brochures, which have been termed proto-labeling, because the Investigator's Brochure is the premarketing forerunner of the product package insert and provides the same types of information as the package insert, including adverse reactions, contraindications, warnings and precautions, to advise physicians and other healthcare practitioners of information important to their safe and effective use of medical products. I have analyzed safety information available from clinical trials, the scientific and medical literature, and postmarketing experience to provide this information to the U.S. Food and Drug Information (FDA) and to physicians and other healthcare practitioners to enable their safe and effective use of medical devices and drugs/biologics. I have submitted safety alerts to FDA and physicians about new and important product safety information.

Additionally, I have prepared marketing materials detailing product information. In so doing, I assured the accuracy and fair balance of the safety and effectiveness information presented. Similarly, I have advised companies on the appropriateness of information in press releases and other corporate documents to ensure any potentially misleading or improper information was excluded.

The above is a brief overview of my professional experience relevant to this Report. Further details are described below.

I have performed due diligence evaluations of potential new products to advise sponsor companies or research institutes on product development requirements, including preclinical and clinical testing needs and also regulatory pathway and strategy. I have managed internal and extramural preclinical research programs required for support of product development and manufacturing, clinical research, and business development activities. These have included product characterization, process improvement, stability studies, bioassay development, pharmacology, and preclinical efficacy studies. Additionally, I have developed product-specific, preclinical toxicology testing plans and protocols and have overseen the conduct and reporting of these studies for FDA-regulated products. I have taught Good Laboratory Practice (GLP), which is the regulatory standard for conducting nonclinical (preclinical) laboratory studies to support applications submitted to FDA for research or marketing authorizations. In addition, I have conducted GLP audits of toxicology testing facilities.

Evaluation of preclinical safety and efficacy data are central considerations before initiating human use. Accordingly, I have designed clinical investigational plans and clinical protocols in consideration of preclinical study results, including both efficacy and toxicology data. As a key member of many product development teams, I have been instrumental in the assessment of preclinical data to determine whether the available safety information supported the transition from preclinical to clinical use. Similarly, I have evaluated both preclinical and available clinical safety data to determine whether product safety profiles supported application for marketing authorization and also product development for new clinical uses.

I have designed and managed or directed the conduct of numerous clinical studies, from first-in-man studies of novel therapeutics and medical devices to pivotal studies for marketing approval. This has included performing and/or directing the monitoring, data management, analysis, and reporting of the safety and effectiveness/efficacy data from these studies, ensuring that all activities were performed in compliance with applicable regulations, Good Clinical Practice (GCP), the international regulatory and quality standard for the conduct of clinical trials involving human subjects and other relevant FDA Guidances. Of note, I established, staffed, and directed the first Clinical Quality Assurance and Document Control department at Amgen, a leading biotechnology firm. Further, I have directed collaborative clinical programs with foreign affiliates to reduce overall clinical development time and costs, and enhance quality and usability of data globally for marketing applications.

I have organized and directed meetings of clinical study physicians ("investigators") at the outset of multicenter clinical trials both to obtain concurrence on complex clinical study designs and endpoints and also to instruct these physician investigators on clinical trial requirements and their obligations to comply with the clinical study protocol, all applicable regulations, and GCP. I have performed compliance (quality assurance) audits of clinical investigators' conduct of clinical trials and advised and worked with them and their clinical study staff to correct any deficiencies identified. With respect to FDA inspections of clinical studies, I have been the sponsor representative with lead responsibility for "hosting" the FDA inspection of a sponsor company and clinical investigative sites.

I have provided consultation to multiple companies to establish or evaluate their processes and procedures and, in the latter case, to implement changes necessary to achieve compliance with regulatory and industry standards. In this role, I have developed standard operating procedures and set up operations to perform all aspects of clinical studies and regulatory affairs, including the following activities, among others: clinical protocol design; writing patient informed consent forms (including all known or potential risk information); writing investigator's brochures or report of prior investigations (the forerunner of the package insert/professional labeling); clinical study monitoring and management; data tracking and management; recordkeeping; and reporting of adverse events, Such procedures at Symbion have undergone quality assurance audits by multiple sponsor companies successfully. Further, I have consulted with a multinational pharmaceutical company both to develop implementation strategy and also to implement a global clinical data management system.

I have managed coding of adverse events (using dictionaries designated for regulatory activities) for worldwide clinical programs for the purpose of safety evaluations and regulatory reporting and have collected, investigated, evaluated, and reported safety data to

fulfill both premarketing and postmarketing regulatory obligations. I have advised physician investigators of updated safety information: (i) in the context of providing updated investigator's brochures (which contain similar contents as eventual, professional product labeling [to the extent of known information], in order to provide for safe and effective use of the investigational product); and (ii) through required serious adverse event reports to advise physicians (as well as FDA) of new, critical safety information concerning serious risks with use of the investigational product. In the postmarketing setting, I also have directed the updating of postmarketing surveillance procedures and audited postmarketing adverse reaction records for regulatory compliance. Additionally, I have evaluated post-marketing utilization data.

I have reviewed or contributed substantially to the development of product labeling, including not only adverse reaction content but also contraindications and warnings, nonclinical toxicology and clinical studies information, and product use instructions. I have prepared product launch "backgrounders" for marketing programs and critically reviewed press releases of sponsor companies and other corporate documents prior to their release to ensure any potentially misleading or improper information is excluded.

I have served as the U.S. Agent or authorized representative for FDA matters for both medical device and drug companies, with responsibility for FDA communications and, in the case of medical device companies, for establishment registration and device listing. I have prepared and made numerous regulatory submissions of multiple types to FDA, including premarketing and postmarketing submissions, both for medical devices and drugs/biologics. Additionally, I have advised sponsor companies regarding a broad scope of regulatory requirements, including adverse event reporting, the content of adverse reactions in labels and corrective and preventive actions to address FDA inspectional findings. I have represented sponsor companies during many face-to-face meetings and teleconferences with FDA.

I have served on the Board of Directors or Advisory Board for multiple organizations, including the Biotechnology and Health Programs Advisory Board, California State University Channel Islands (CSUCI); the Clinical Trials Certificate Program Advisory Board, California State University Program for Education and Research in Biotechnology (CSUPERB); and CompassioNow (formerly CareNow Foundation, the purpose of which is to provide medical care to the world's least served). At CSUCI, I also have served as an Advisor for the Master of Science in Biotechnology (MS Biotech) team projects, a curriculum requirement in an academic or industrial location. I have developed and am the instructor for a graduate level course titled "Clinical Trials and Quality Assurance" in the CSUCI MS Biotech program curriculum. As part of this course, I instruct my students on ethics in medical product development and the importance of obtaining and evaluating adequate preclinical safety data before transitioning to human use and assign them case studies relevant to this topic for critical evaluation and class presentation. Additionally, I have developed and am the instructor for a course titled "Clinical Trials Project Management: Managing Clinical Trials" for graduate level students enrolled in either the Program for Applied Biotechnology Studies or the Certificate in Clinical Trials Project Management Program at California State University, Fullerton. I also have served as guest lecturer for the MS Biotech program, CSUCI.

I have often been an invited speaker at industry conferences or workshops on topics current to the development of medical devices, drugs and biologics and have often provided instruction on Good Clinical Practice and other medical product development topics: at sponsor-company, in-house training programs; workshops and seminars; as a guest lecturer and instructor in university graduate or professional programs (as discussed above). I founded the Drug Information Association (DIA) Sub-group and Advisory Committee on Biotechnology and chaired DIA workshops on biotechnology in 1991 and thereafter from 1993 annually through 2001. I have served on the Regulatory Training Course Faculty for the Drug Information Association. I have been an instructor on the medical device premarketing regulations (2008-2009) and postmarketing regulations (2009) for the Orange County Regulatory Affairs Discussion Group (OCRA) course for regulatory professionals preparing to take the U.S. Regulatory Affairs Certification (RAC) examination.

I am RAC-certified, which means I hold the U.S. Regulatory Affairs Certification (RAC, certifying knowledge of U.S. regulations). The RAC credential is the only certification specifically for regulatory professionals in the healthcare product sector. It is conferred by the Regulatory Affairs Professional Society (RAPS) upon successful performance on a standardized proficiency exam, and in consideration of the applicant's education, training, and overall experience. Continuing education and assumption of leadership roles in the profession are necessary to maintain recertification, which is granted every three years, upon submission of appropriate justification. In addition to maintaining the RAC credential, in 2009 I was named a RAPS Fellow (FRAPS), a peer-reviewed credential that recognizes senior regulatory professionals based on experience, contributions, and leadership in the regulatory profession.

In sum, I have the peer-reviewed qualifications of a RAPS Fellow based on professional experience, credentials, and training. Being RAPS certified[1] and a RAPS Fellow,[2] I have achieved the highest level experience within my profession, Level IV, as outlined in the Regulatory Affairs Professional Development Framework.[3]

I earned a Bachelor of Science degree, *magna cum laude*, in Microbiology from Louisiana Polytechnic University and a Doctor of Philosophy (PhD) degree in Toxicology, with a Pharmacology minor, from Indiana University (Medical School campus). I performed my doctoral research predominantly at the Eli Lilly Laboratory for Clinical Research in Indianapolis, Indiana. My doctoral research included the planning and hands-on conduct of all aspects of three clinical pharmacology and toxicology studies. As the prior valedictorian for my high school, I

[1]I tested for and achieved RAPS's Regulatory Affairs Certification ("RAC"). The development of the RAC examination and selection process was based upon extensive research on the scope of practice and specific activities of the profession. This research has been replicated and updated several times, with studies extended to professionals involved with the European, US, and Canadian regulatory systems.

[2]The program recognizes professionals with over 15 years of regulatory experience for their significant contributions and leadership. Fellows receive a prestigious status and serve as important resources for strategic dialogue, mentoring, implementation of special initiatives, and international development. RAPS Fellows, *available at* http://www.raps.org/membership-amp-benefits/raps-fellows.aspx (last visited Feb. 24, 2012).

[3]The Regulatory Affairs Professional Development Framework offers a model for describing the basic body of knowledge and relevant skills of the RA profession across product lines, geographic locations and employer types at four major career stages. The skills, knowledge, and experience that I provide are reflected in this research-driven whitepaper.

was recognized in 2008 for my career accomplishments by induction to the Bossier High School Alumni Hall of Fame.

A copy of my current Curriculum Vitae is attached as Appendix A.

B. Methodology

I have been asked to address the actions of Ethicon, Inc., Ethicon Women's Health and Urology, a Division of Ethicon, Inc., Gynecare, and Johnson & Johnson (collectively referred to as Ethicon) in the context of the company's regulatory responsibilities as the manufacturer of the medical device GYNECARE Tension Free Vaginal Tape System (referred to as TVT™ Retropubic System, TVT or TVT Classic), indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. All of my opinions expressed in this Report are offered to a reasonable degree of scientific and professional certainty.

During the preparation of this Report, I reviewed, consulted, and relied upon the following categories of information, listings of which are provided in Appendix B:

a) Applicable statutes, regulations and guidance documents;
b) 510(k) Premarket Notifications, Numbers K974098 and K012628, and related Ethicon and FDA correspondence;
c) Other 510(k) Summaries relevant to the TVT regulatory history;
d) Other Ethicon documents of multiple types produced in this litigation;
e) Documents located by specifically directed independent on-line searches;
f) Relevant scientific and medical literature (See Appendix C);
g) Deposition transcripts of Dr. Axel Arnaud, Dr. Piet Hinoul, Dr. Martin Weisberg, Dr. David Robinson, Catherine Beath, Susan Lin, Gregory Jones, Daniel Smith, Boris Batke, Christophe Vailhe, Dr. Joerg Holste, and Daniel Burkley; Dan Lamont, Laura Angelini, and Bryan Lisa;
h) Ethicon website for Gynecare TVT™ Retropubic System; and
i) FDA website, including the searchable 510(k) database; the Manufacturer and User Facility Device Experience (MAUDE) Database for reports of serious adverse events; FDA's advisories and actions to address the safety issues associated with transvaginal mesh products for pelvic organ prolapse, e.g., FDA's 2008 *Public Health Notification*, 2011 *Safety Communication*, and 2011 Medical Devices Advisory Committee meeting of the Obstetrics and Gynecology Medical Devices Panel; Warning Letters.

A number of these documents are cited in footnotes throughout this Report as primary reference materials.

In reaching my opinions, based on my review, critical evaluation, synthesis, integration, and analysis of the body of relevant evidence, I brought to bear my educational background, professional training, and experience in the fields of regulatory affairs and medical product research and development, including nonclinical and clinical testing to determine medical

product safety and efficacy. I also drew upon the real world lessons learned from my industry experience.

The methodology I employed and level of scrutiny applied to the totality of the evidence in this matter and in the preparation of this Report are no different than those used in my practice over the course of my career as an expert in regulatory affairs and medical product research and development, including the testing and evaluation of medical product safety and efficacy, and as a researcher, educator, and scientist in general. Essentially, I conducted background research, constructed theories, tested those theories against the information I reviewed and the industry standards of which I am aware through my knowledge, experience, and training, analyzed my findings, and communicated my conclusions herein.

I conducted comprehensive observations and analysis of the totality of the categories of information listed above. I employed logical reasoning to my findings and formed conclusions, which are validated by information in the documentation and deposition records. I drew conclusions from my observations based on my extensive and specialized experience. . My opinions are grounded in well-established techniques, processes, and methods. They reflect practices commonly undertaken in the medical device industry within the context of the applicable federal regulatory scheme that informs and guides industry standards and conduct.

II. U.S. STATUTORY AND REGULATORY AUTHORITY: BASIS FOR OPINIONS

The purpose of this Section is to establish the regulatory and scientific foundation on which my professional opinions are based and set forth in this Report. Thus, I will provide a brief overview of FDA's authority to regulate medical devices, and the manufacturer's responsibility to comply with applicable regulations. I will describe device classifications and the corresponding premarket submissions required in order for a manufacturer to obtain FDA's authorization to sell a medical device in the U.S. I will complete this Section with a detailed explanation of a device manufacturer's postmarket responsibilities concerning (i) labeling and advertising and (ii) postmarket vigilance, or surveillance.

A. FDA Authority and Manufacturer Regulatory Compliance

The U.S. Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) is responsible for regulatory oversight of the manufacture, sale, and distribution of medical devices in the United States under authority of the Federal Food, Drug, and Cosmetic Act (FDCA). Within the FDA, the Center for Devices and Radiological Health (CDRH) is the center that has the responsibility to develop and implement regulations for the purpose of protecting the public health in the field of medical devices. Ensuring optimum safety and device effectiveness, however, requires the cooperation of all stakeholders involved in the life cycle of a medical device: the manufacturer, FDA, and the end users. Each has a specific role to play in risk management. It is also important to remember that the FDA regulations are minimum standards, and where safety or effectiveness is an issue, the manufacturer bears the ultimate responsibility of ensuring the safety and effectiveness of its devices.

The medical device manufacturer means any person who designs, manufactures, fabricates, assembles, or processes a finished device.[4] The term "person" includes individual, partnership, corporation, and association.[5] Manufacture, preparation, propagation, compounding, assembly, or processing of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in Section 201(h) of the FDCA:[6] an article intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body but which does not achieve its primary intended purposes through chemical action and is not dependent upon being metabolized to achieve its primary intended purposes.

The FDA does not design and conduct either nonclinical or clinical studies to support device safety and effectiveness; it will advise on the adequacy of studies proposed by the manufacturer and then review the completed study results and other information submitted to FDA to determine if the materials submitted support the safety and effectiveness of the device sufficiently to clear or approve the device for sale for the requested indication(s) for use. Importantly, the FDA's capacity to monitor every single medical device, or drug/biologic, postmarketing is limited. There are more than 20,000 companies worldwide that produce over 80,000 brands and models of medical devices in the U.S. marketplace, according to CDRH.[7] That is why FDA depends on the cooperation and good faith of the device manufacturer to comply with FDA's regulatory decisions and applicable FDA regulations. It is the manufacturer's responsibility to ensure its devices are labeled and marketed in compliance with applicable FDA regulations.

While the FDA maintains a passive postmarketing surveillance system for safety concerns, the limitations of such a system underscore why the manufacturer is responsible for implementing a postmarket vigilance (surveillance) program. Specifically, the manufacturer must investigate and report to the FDA all serious or life-threatening adverse events about which it becomes aware if there is a reasonable suggestion that the manufacturer's device may have caused or contributed to such events. If the manufacturer becomes aware of the "need for remedial action from any information, including any trend analysis" in order "to prevent an unreasonable risk of substantial harm to the public health," the manufacturer must report such information to the FDA immediately (i.e., within five work days after becoming aware of the event).[8] The manufacturer must also maintain systems that ensure access to such adverse event information for timely follow-up and FDA inspection.[9]

In recent years, the FDA's authority and its capacity to discharge its responsibilities have been reviewed by independent agencies, including the Institute of Medicine and the Government Accountability Office (GAO). Summarily, these reports have recognized that FDA lacks the capacity to provide adequate oversight. While FDA continues efforts to address its increasingly

[4] 21 CFR § 820.3(o).
[5] Section 201(e) of the Federal Food, Drug, and Cosmetic Act (FDCA).
[6] 21 CFR § 807.3(d).
[7] AdvaMed (Advanced Medical Technology Association). The 510(k) Process: The Key to Effective Device Regulation, 8/19/08, p.2.
[8] 21 CFR § 803.53(a).
[9] 21 CFR § 803.17(b)(4).

complex public health mission of assuring medical product safety, effectiveness, and quality, the findings in these reports further emphasize why it is of critical importance for the device manufacturer to act in good faith at all times to ensure compliance with its responsibilities, as set forth in the applicable regulations, to prevent unnecessary risk to the public health.

The FDA provides multiple alternative avenues to medical device companies to assist them in interpreting any perceived grey areas in the regulations. Reasonably prudent medical device manufacturers avail themselves of these avenues provided by the FDA to ensure compliance, particularly when a question arises as to the proper course of regulatory action. These multiple alternative avenues include guidance documents and the ability to call the FDA, email the FDA, and meet with the FDA. In addition, reasonably prudent medical device manufacturers are always expected to err on the side of caution, i.e., regulatory compliance, when faced with any uncertainty or ambiguity in the regulations.

B. Device Classifications

FDA classifies medical devices into one of three regulatory classes based on the level of risk associated with use of the device and the level of control necessary to reasonably assure that the device is safe and effective for its intended use. Devices posing the lowest risk are placed in Class I and are subject to the least regulatory control. Class I devices, such as elastic bandages and tongue depressors, present minimal potential for harm to the user and are subject to the "General Controls" applicable to all medical devices. General Controls are the basic provisions of the 1976 Medical Device Amendments to the FDCA that provide the FDA with the means of regulating devices to ensure their safety and effectiveness. General Controls include provisions for adulteration, misbranding, establishment registration and device listing, premarket notification [510(k)], records and reports, and Good Manufacturing Practices/Quality System Regulation (QSR), among others.[10]

Class II devices pose incrementally greater risk such that the General Controls are not sufficient to provide reasonable assurance of safety and effectiveness. Class II devices are subject to "Special Controls" in addition to General Controls. Special Controls may include labeling requirements, performance standards, postmarket surveillance studies, or other controls the Agency deems necessary to provide reasonable assurance of the safety and effectiveness of the device. Ethicon's TVT System is a Class II device. Electrocardiographs and powered bone drills are other examples of Class II medical devices. Highest-risk devices, such as some implants and life-supporting devices, are placed in Class III and generally are subject to Premarket Approval (PMA), which is discussed below, and means that an application must be submitted to and approved by FDA before the device may be legally marketed.

C. The PreMarket Review Process: 510(k) vs. PMA

In general, unless exempt under FDA regulations, devices are subject to one of two types of FDA premarket review before they may be legally marketed in the United States. Class I and II devices subject to premarket review are required to obtain FDA clearance through the premarket notification, or 510(k) process; Class III devices are required to obtain FDA approval through the

[10] 21 CFR § 860.3; Device Advice – General Controls for Medical Devices, US FDA/CDRH.

more stringent PMA process. (There is a third but infrequently used alternative, the Product Development Protocol [PDP], which combines plans for an Investigational Device Exemption [IDE] to conduct a clinical trial.) Most Class I devices and a few Class II devices are exempt from the 510(k) requirements but are not exempt from other General Controls, which are discussed in Section II.B. above. All medical devices must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled, and have establishment registration and device listing forms on file with the FDA.[11]

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, i.e., substantially equivalent (SE), as a legally marketed device. Legally marketed devices, in this context, include any device that was legally marketed prior to May 28, 1976 (i.e., a preamendments device), for which a PMA is not required, and any device which has been found SE through the 510(k) process.[12] To support substantial equivalence claims, the device that is the subject of a 510(k) must be compared to one or more similar legally marketed devices, commonly referred to as "predicate(s)." A claim of substantial equivalence does not mean the new and predicate device(s) must be identical. SE is established with respect to intended use, design, materials, manufacturing process, performance, safety, effectiveness, labeling, standards, and other characteristics, as applicable. While clinical trials generally are not necessary for 510(k) submissions, FDA may require the conduct of clinical trials to substantiate the safety and effectiveness of a device in approximately 10-15% of cases and also may require postmarket surveillance to obtain 510(k) clearance.

In addition to the traditional method of demonstrating substantial equivalence under section 510(k) of the FDCA, there are two alternative approaches that may be used, under appropriate circumstances, to demonstrate substantial equivalence: (i) "Special 510(k): Device Modification" option, which utilizes certain aspects of the Quality System Regulation, and (ii) "Abbreviated 510(k)" option, which relies on the use of guidance documents, special controls, and recognized standards to facilitate 510(k) review. In accordance with the Quality System Regulation,[13] manufacturers must establish and follow a systematic set of pre-production design controls when initially designing medical devices or when making subsequent modifications to those designs. If a manufacturer is intending to modify its own legally marketed device and the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device, then summary information that results from the design control process can serve as the basis for 510(k) clearance, and the "Special 510(k): Device Modification" option may be utilized.[14]

Further, FDA has provided guidance to assist the medical device manufacturer to decide when a change to an existing device already in commercial distribution represents a significant change that requires a 510(k) premarket notification,[15] i.e., a change that could significantly affect the

[11] Device Advice – Class I/II Exemptions, US FDA/CDRH.
[12] 21 CFR § 807.92(a)(3).
[13] 21 CFR Part 820: Quality System Regulation.
[14] The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance, US FDA/CDRH, March 20, 1998.
[15] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997.

safety or effectiveness of the device or a major change in the intended use of the device.[16] "The type of modifications addressed in the draft guidance includes labeling changes, technology or performance specifications changes, and materials changes. When making the decision on whether to submit a 510(k), the manufacturer's basis for comparison of any changed device should be the device described by the cleared 510(k). The guidance includes a main flowchart to help manufacturers through the logic scheme necessary to arrive at a decision on when to submit a 510(k) for a change to an existing device. If a manufacturer's consideration of all proposed changes results in a decision that a 510(k) submission is not required, they should document the basis for the decision, including the application of the flowchart model, along with the necessary records of the validation of changes to the device. In those circumstances where the proposed change is not addressed in the flowchart or in a device-specific guidance document, manufacturers are encouraged to contact the Office of Device Evaluation in CDRH to find out whether other, specific guidance exists or if additional help is available."[17]

Following submission of a 510(k), the subject device may not be marketed in the U.S. until the 510(k) applicant receives a letter (i.e., order) declaring the device substantially equivalent, thereby "clearing" the device for marketing. This is an important distinction in that the device is not technically "approved" by the FDA as with a PMA but instead is said to be cleared, or 510(k)-cleared, for marketing. A substantially equivalent determination means that the new device is at least as safe and effective as the predicate(s), specifically, that the new device has:

(1) The same intended use and the same technological characteristics as the predicate(s);
or
(2) The same intended use and different technological characteristics, and the information submitted to FDA:
   a. Does not raise new questions of safety and effectiveness; and
   b. Demonstrates that the new device is at least as safe and effective as the predicate device(s).

Technically, by regulation[18] the FDA has 90 days to review the 510(k) and issue a SE or not substantially equivalent (NSE) determination. If the FDA determines that a device is NSE (novel), it is considered Class III and will require a PMA prior to marketing. At this point, the 510(k) sponsor has the following options: (1) cease plans to market the device; (2) request reclassification; (3) submit a request for evaluation of the automatic Class III designation; (4) present new evidence (data) in support of a 510(k) clearance; or (5) proceed to develop the device through the PMA route. A Class II device that is introduced into commercial distribution without a required 510(k) clearance is considered "adulterated" and "misbranded" and subject to regulatory sanctions.

[16] 21 CFR § 807.81(a)(3).
[17] FDA Guidance: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1), January 10, 1997.
[18] 21 CFR Part 807.

A PMA application is generally considered to be a more rigorous process than the 510(k) and is analogous to the New Drug Application (NDA) or Biologics License Application (BLA) that must be submitted for review and approval prior to marketing for drugs and biologics, respectively. The PMA is generally required for Class III devices that are determined to be either novel or that pose a significant risk of illness or injury.[19] Approval hinges on a demonstration of safety and effectiveness through the presentation of valid scientific evidence. Most often, this path requires the conduct of prospective controlled clinical trials conducted in accordance with the strict Good Clinical Practice (GCP) standards established by the FDA and the International Community. By regulation[20], the FDA has 180 days to review a PMA and issue a decision concerning approval of the application. In general, a Class III device that is introduced into commercial distribution without an approved PMA is considered "adulterated" and "misbranded" and subject to regulatory sanctions.

D. Determination of Substantial Equivalency

Although the manufacturer may submit any form of evidence to the Food and Drug Administration in an attempt to substantiate that a device is substantially equivalent to a predicate device, the device manufacturer is supposed to rely upon only valid scientific evidence.. Valid scientific evidence may include evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Note that the 510(k) process only requires that a new device demonstrate "substantial equivalence" to a previously cleared device or device marketed before 1976 ("predicate" device). Products cleared via the 510(k) process are not required to demonstrate safety and effectiveness, but substantial equivalence is taken to mean that the new device is "at least as safe and effective" as the predicate.[21] This is in contrast to the Premarket Approval process, which is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

E. Device Label, Labeling, Advertising, and Misbranding

The General Controls applicable to all devices include provisions for proper labeling and misbranding. The Federal Food, Drug and Cosmetic Act (FDCA) is the law that applies to manufacturers for labeling and advertising violations concerning products it regulates. The following are standard terms and principles used within the medical device industry and applied in industry practice. These form the basic building blocks for industry to establish governing standards of practice and are built upon through application of experience, training, and as circumstances dictate.

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[19] 21 CFR Part 814.
[20] 21 CFR § 814.40.
[21] Medical Devices: How to Market Your Device, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/

1. Applicable Definitions

The laws enacted by the U.S. Congress concerning products regulated by the FDA are implemented by the FDA as enforceable regulations. Together, these laws and implementing regulations define the terms that are applicable to device labeling, advertising, and misbranding. Some of the terms that are significant for purposes of this Report include the following.

1.1 Label: Section 201(k) [21 U.S.C. 321(k)] of the FDCA defines "label" as a:

> "display of written, printed, or graphic matter upon the immediate container of any article..."

The term "immediate container" does not include package liners. Any word, statement, or other information appearing on the immediate container must also appear "on the outside container or wrapper, if any there be, of the retail package of such article," or must be "easily legible through the outside container or wrapper."

1.2 Labeling: Section 201(m) [21 U.S.C. 321(m)] of the FDCA defines "labeling" as:

> "all labels and other written, printed, or graphic matter
> (1) upon any article or any of its containers or wrappers, or
> (2) accompanying such article" at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.

The term "accompanying" is interpreted liberally to mean more than physical association with the product. It extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, etc. "Accompanying" also includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.[22] Training and instructional videos are considered labeling. Websites are also considered under this broad definition of labeling, and the statements a manufacturer makes about its product on websites are regulated as labeling and must be truthful and accurate.

1.3 Indications for Use

The general statement of "Indications for Use" identifies the target population in a significant portion of which sufficient valid scientific evidence has demonstrated that the device as labeled will provide clinically significant results and at the same time does not present an unreasonable risk of illness or injury associated with the use of the device.[23]

1.4 Intended Uses

The term "intended uses" refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the

[22] Device Advice – Labeling Requirements, US FDA/CDRH.
[23] Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo.

circumstances surrounding the distribution of the device. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such representatives. It may be shown by the offering or the using of the device, with the knowledge of such persons or their representatives, for a purpose for which it is neither labeled nor advertised.[24]

1.5 Contraindications

This term refers to situations in which the device should not be used because the risk of use clearly outweighs any possible benefit. Known hazards and not theoretical possibilities are to be listed as contraindications. For example, if hypersensitivity to an ingredient in the device has not been demonstrated, it should not be listed as a contraindication.[25] Furthermore, should a medical device manufacturer have information that its medical device does not perform well in certain patient populations, it should list that information in the contraindications section.

1.6 Directions for Use (DFU) (or Instructions for Use [IFU])

This means the providing of directions to the practitioner or layman (e.g., patient), as appropriate, so that s/he can use the device safely and for the purposes for which it is intended. "Directions for Use" also include indications for use and appropriate contraindications, warnings, precautions, and adverse reaction information. Directions for Use requirements applicable to prescription devices appear throughout 21 CFR Part 801.[26]

1.7 Fair Balance

For advertising and promotional materials, this term means that advertisements must communicate fairly and in a balanced manner information relating to side effects and contraindications and information relating to effectiveness of the product.[27] In other words, information about side effects and contraindications must be comparable in depth and detail with claims for safety and effectiveness.

1.8 Prescription Device

By definition under 21 CFR § 801.109, this is a device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe except under the supervision of a practitioner licensed by law to direct the use of the device, and hence for which "adequate directions for use"[28] cannot be prepared.

[24] 21 CFR § 801.4; Device Labeling Guidance 3/8/91 (G91-1) – Blue Book Memo.
[25] *Id.*
[26] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[27] 21 CFR §§ 202.1(e)(5) and (6).
[28] 21 CFR § 801.5.

2. ***General Device Labeling: 21 CFR Part 801***

General labeling requirements for medical devices have been established in 21 CFR Part 801. Guidance on "Indications for Use," "Contraindications," "Warnings," "Precautions," and "Adverse Reactions" paraphrase applicable provisions in the labeling requirements for prescription drugs.[29]

A premarket notification must normally only contain proposed labeling sufficient to describe the device's intended use, as discussed in the "Blue Book" 510(k) Memorandum #K86-3 dated June 30, 1986.[30] Accordingly, a 510(k) finding of substantial equivalence does not connote approval of the proposed labeling. However, in the case of devices with special labeling requirements and devices for which inclusion of specific directions for use, contraindications, warnings, etc., in the labeling may be critical to a finding of equivalence, CDRH's Office of Device Evaluation (ODE) 510(k) labeling review includes an evaluation of compliance of the proposed labeling or portions thereof, as appropriate.

In contrast, specific labeling is approved as part of a PMA. While FDA will approve a PMA on the basis of draft final labeling if the only deficiencies concern editorial or similar minor deficiencies in the draft final labeling, PMA approval depends on incorporation of the specific labeling changes exactly as directed and the manufacturer is required to submit to FDA a copy of the final printed labeling before marketing.[31] Labeling changes that affect the safety or effectiveness of a device require a PMA supplement and can be done without FDA approval via a Special PMA Supplement only when such modifications are based on newly acquired information and evidence of a causal relationship between the product and a safety signal. New information "must reveal risks of a different type or greater severity or frequency than previously included in submissions."[32,33] Importantly, routine review of patient labeling for all original PMAs and panel-track supplements will be conducted by the FDA Division of Device User Programs and Systems Analysis (DDUPSA) when human factors for the usability of the device need to be considered.[34]

3. ***Patient Labeling***

FDA issued a guidance in April 2001, titled "Guidance on Medical Device Patient Labeling," to assist manufacturers in their development and FDA reviewers in their review and evaluation of patient labeling, "to help make it understandable to and usable by patients," and lay caregivers as applicable.[35] Medical device patient labeling is any information associated with a device

[29] 21 CFR Part 201; Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[30] Guidance on the CDRH Premarket Notification Review Program 6/30/86 [K86-3]: 510(k) Memorandum #K86-3.
[31] FDA Device Advice: Device Regulation and Guidance. PMA Labeling http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050390.htm.
[32] 21 CFR § 814.39 PMA Supplements.
[33] Modifications to Devices Subject to Premarket Approval (PMA)-The PMA Supplement Decision. Dec 11, 2008 http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089274.htm#4e.
[34] FDA Memorandum of Understanding Regarding Patient Labeling Review (Blue Book Memo #69-3).
[35] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.

targeted to the patient or lay caregiver. It is intended to help assure that the device is used safely and effectively. This labeling may pertain to therapeutic, restorative, diagnostic, or cosmetic devices.

Medical device patient labeling is supplied in many formats, **for example, as patient brochures,** patient leaflets, user manuals, and videotapes.[36] [Emphasis added] This labeling is intended to be supplied, or given to and used by patients or their lay caregivers with or without accompanying professional counseling. **Medical device patient labeling may accompany devices intended solely for physicians to operate**, devices for both physicians and patients or lay caregivers to operate, and devices operated solely by patients or their lay caregivers. [Emphasis added.]

Medical device patient labeling should be supplied whenever it can benefit patients or lay caregivers by increasing their knowledge about the device. The informational needs of the target audience should be known in order to determine if patient labeling is necessary, e.g., whether patients need or want specific information, whether there is something unique about the device that needs to be explained to the patient, and whether patients already know the information.

Providing risk/benefit information is important when patients or lay caregivers need to:

- select among similar devices or device procedures;
- be involved in deciding whether to have a procedure involving the device; and/or
- understand the effect or influence of the device on the patient or others.

Risk/benefit information is particularly pertinent to patients considering the implantation of synthetic, biosynthetic or biological meshes for vaginal prolapse, versus non-mesh repair.

4. The Meaning of Intended Use

To determine whether or not a new device has the same intended use as a predicate device, CDRH assesses any difference in label indications based on the safety and effectiveness questions they may raise. As described in Section II.C., "same intended use" is a key determinant in assessment of substantial equivalence. CDRH considers such points as condition or disease to be treated or parts of the body or types of tissue involved, etc. If a new device is determined to have the same intended use, CDRH may then proceed to determine whether or not it is substantially equivalent. Devices that do not have the same intended use cannot be substantially equivalent.[37]

5. Promotion and Intended Use

Products are cleared or approved for certain intended uses. Change in Intended Use may require a new clearance or approval. New Intended Use can be created by:

[36] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[37] Guidance on the CDRH Premarket Notification Review Program 6/30/86 [K86-3]: 510(k) Memorandum #K86-3.

(1) Labeling, advertising, or promotional claims;
(2) Oral statements;
(3) Manifestations of objective intent;[38]
(4) Expressions;
(5) Circumstances of distribution; and
(6) Offering with knowledge of use.[39]

6. Labeling and Advertising (General Device Labeling: 21 CFR Part 801)

The distinction between labeling and advertising, both of which draw attention to the article to be sold, is often superficial or nebulous. Both are used for a similar purpose, i.e., to provide information about the product. Thus, according to an appellate court decision, "[m]ost, if not all, labeling is advertising. The term 'labeling' is defined in the FDCA as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."[40]

While advertising and promotion are not defined in the FDCA and FDA regulations for medical devices, FDA interprets any activity used by the sponsor to create an interest in the company's products, including the Internet, as advertising.[41] It is noteworthy that FDA has defined prescription-drug advertising as including "advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems."[42]

Jurisdiction over medical device advertising is split between the FDA and the Federal Trade Commission (FTC). The FTC has primary oversight responsibility for the advertising of non-restricted devices. The FTC prohibits advertising that is false and misleading and requires substantiation of all claims that are made in advertisements.[43] With regard to the advertising of medical devices, the FTC has defined substantiation as requiring balanced, scientific evidence in the form of well-controlled clinical studies.

Except in extraordinary circumstances, FDA cannot require prior approval of the content of any advertisement except in the case of any printed matter which FDA determines to be labeling as defined in Section 201(m) of the FDCA.[44] In practice, many items that could meet the definition of "advertising" also meet the definition of "labeling" and are regulated by FDA as labeling.

7. Misbranding

Section 502 of the FDCA (21 U.S.C. § 352) contains provisions on misbranding and false or misleading labeling. A device is misbranded if:

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[38] 21 CFR §§ 201.128, 801.4.
[39] 21 CFR § 801.4.
[40] *United States v. Research Laboratories, Inc.*, 126 F.2d 42, 45 (9th Cir. 1942), *cert. denied*, 317 US 656 (1942).
[41] FDA Docket No. 2005N-0354.
[42] 21 CFR § 202(l)(1).
[43] 15 U.S.C. § 45.
[44] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.

(1) Its labeling is false or misleading in any particular;[45]
(2) Its advertising is false or misleading in any particular;[46]
(3) It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling;[47]
(4) Its labeling does not bear adequate warnings;[48]
(5) There is a failure to furnish any materials or information requested by or under Section 519 of the FDCA on reports and records;[49] and
(6) There is a failure to have a necessary 510(k) clearance.[50]

Pursuant to the FDCA § 201(n), a device is misbranded when there is a failure to reveal material facts.

In summary, prescription medical devices such as Ethicon's TVT System are misbranded if their labels do not bear information for use including indications, effects, routes, methods, frequency and duration of administration (as applicable), and any relevant hazards, contraindications, side effects and precautions under which practitioners licensed by law to administer the devices can use them safely and for the purpose for which they are intended, including all purposes for which they are advertised or represented,[51] or if there is a failure to obtain the necessary 510(k) clearance.

A medical device may be misbranded not only if the actual label contains false or misleading representations, but also if the device's advertising fails to reveal facts material to the representations made or consequences that may result from the use of the product under the conditions of use prescribed in the labeling or advertising or under such conditions of use as are customary or usual.[52] Labeling and advertising must therefore present a fair balance of information relating to the side effects and effectiveness of the product.

8. False or Misleading Labeling

The phrase "false or misleading" is not confined in meaning to untrue, forged, fraudulent, or deceptive. The word "misleading" in the FDCA means that labeling is deceptive if it creates or leads to a false impression in the mind of the reader. A "false impression" may result not only from a false deceptive statement, but may also be instilled in the mind of the consumer by ambiguity, misdirection, or failure to inform the consumer of facts that are relevant to those statements actually made**. In other words, the label that remains silent as to certain consequences may be as deceptive as the label that contains extravagant claims.**[53]

[45] FDCA § 502(a).
[46] FDCA § 502(j).
[47] 21 U.S.C. § 352.
[48] FDCA § 502(f)(2).
[49] FDCA § 502(t).
[50] FDCA § 502(o).
[51] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[52] 21 U.S.C. § 321(n).
[53] Device Advice – Labeling Requirements: Misbranding, US FDA/CDRH.

Examples of false or misleading labeling include, among others:

(1) Unsubstantiated claims of therapeutic value;
(2) Expression of opinion or subjective statements; and
(3) Failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion.[54]

9. Warnings

Product labeling is a primary cornerstone of managing product safety, because communication of serious risk is critical to prevent or mitigate product risk. Thus, labeling content, including warning statements when required to protect users, is a key factor in determining whether there is reasonable assurance that a device is safe and effective for its intended use.

Warning statements on "Instructions for Use" should be delineated by underlining, bold print, boxing, etc. The purpose of "Warnings" is to describe serious adverse reactions and potential safety hazards, the limitations of device use due to such concerns, and steps that should be taken if they occur. A causal relationship need not have been proved.

As discussed in FDA's guidance document titled "Guidance on Medical Device Patient Labeling," there are four elements generally recognized by the courts and research as necessary for an effective warning:

(1) Signal word, i.e., WARNING;
(2) Hazard avoidance directive to give clear instructions to the user on how to avoid the hazard;
(3) Clear statement of the nature of the hazard associated with the warning that characterizes the severity and the likelihood; and
(4) Consequences, specifying the serious adverse events, potential safety hazards and limitations in device use that result if users do not follow instructions.[55]

In other words, for patient labeling, warnings must be set forth in plain language in a manner designed to be understood by the lay person without a medical background. A warning is insufficient if the reader does not understand or appreciate the consequences of failure to comply with the Warning. Hazard alert research has shown that giving a clear idea of the risk has a significant effect on readers.[56]

10. Dear Doctor, or Dear Health Care Professional, Letters

The Center for Drug Evaluation and Research, Manual of Policies and Procedures MAPP 6020.10 is entitled "Dear Health Care Professional" (DHCP) letters and applies specifically to those DHCP letters that concern information about significant hazard to health and/or important

[54] Device Advice – Labeling Requirements: Misbranding, US FDA/CDRH.
[55] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[56] *Id.*

changes in package labeling.[57] FDA issued a new Draft Guidance in November 2010 titled "Dear Health Care Provider Letters: Improving Communication of Important Safety Information."[58] This Guidance provides recommendations to industry and FDA staff on the content and format of DHCP letters, which are correspondence, usually in the form of a mass mailing from the manufacturer or distributor, to alert physicians and other health care providers responsible for patient care about important new information regarding a human drug or biologic (hereafter "drug").

While the cited policy and guidance are designed for drugs, the policies discussed are equally applicable for medical devices. For example, the overall concepts of the July 2007 Guidance for Industry and Staff titled "Writing *Dear Doctor* Letters for Recalls of Implantable Cardioverter Defibrillators (ICDs)"[59] are reflective of the general policies discussed in the referenced drug policy and guidance documents. Moreover, this guidance states that some of its concepts may be appropriately applied to other implanted devices and, importantly, that the recommendations in the guidance draw from "FDA's own research, risk communication principles, and other efforts to standardize the information in *Dear Doctor* letters."

The drug policy makes clear that the FDA may or may not be involved in reviewing DHCP letters before they are mailed. In other words, a company may send out a Dear Health Care Professional letter without approval from the FDA in the event that the company believes that a significant health hazard may endanger patients or that an important labeling change needs to be seen by physicians. Nevertheless, as stated in the new Draft Guidance, FDA believes that effective communication of important new information in DHCP letters can best be accomplished if FDA and the manufacturer work together.

F. Quality System Regulation (QSR) and Design Controls

The 1976 Medical Device Amendments to the FDCA provided for FDA to prescribe Good Manufacturing Practice (GMP) requirements to ensure that medical devices are consistently manufactured according to written specifications and are safe and effective for their intended use. The original GMP regulation became effective on December 18, 1978. In 1990, FDA initiated efforts to revise the regulation due to a large number of device failures and recalls resulting from design defects. The Safe Medical Devices Act of 1990 (SMDA) amended Section 520(f) of the FDCA, providing FDA with the authority to require design controls as part of the GMP regulation. On October 7, 1996, FDA revised the GMP regulation with publication of the Quality System Regulation (QSR), which became effective June 1, 1997. The QSR[60] requires medical device manufacturers to implement and comply with procedures covering the following broad areas: quality system requirements; design controls; document controls; purchasing controls; identification and traceability; production and process controls; acceptance activities; nonconforming product; corrective and preventive action; labeling and package

[57] Manual of Policies and Procedures MAPP 6020.10: NDAs: "Dear Health care Professional" Letters, effective date 7/2/03, issued by CDER, FDA.
[58] Guidance for Industry and FDA Staff: Dear Health Care Provider Letters: Improving Communication of Important Safety Information, issued November 2010, CDER/CBER, FDA.
[59] Guidance for Industry and FDA Staff: Writing *Dear Doctor* Letters for Recalls of Implantable Cardioverter Defibrillators (ICDs), issued July 19, 2007 by CDRH, FDA.
[60] 21 CFR Part 820.

control; handling, storage, distribution, and installation; records; servicing; and statistical techniques. Of particular importance to the subject matter of this Report and thus discussed below are the quality system requirements, design controls, and complaint files (latter addressed in the QSR under Subpart M, Records).

1. Quality System Requirements

The manufacturer is required to establish and maintain a quality system appropriate for the medical devices it designs and manufactures.[61] It is the responsibility of executive management to establish the quality policy and commitment to achieving quality at all levels of the organization.[62] Among management's other responsibilities is the requirement to establish a quality plan that defines the practices, resources, and activities necessary to meet quality requirements.[63] The suitability and effectiveness of the quality system must be reviewed frequently enough to ensure that the company's quality system is in compliance with QSR requirements. Effectiveness of the quality system is required to be monitored through the conduct of periodic audits, the results of which must be reviewed by management with executive responsibility.[64] Further, the QSR emphasizes that appropriately educated and adequately trained and experienced personnel are necessary to assure that an effective quality system is not only established but maintained.[65]

2. Design Controls

Design control requirements apply to all Class II and Class III medical devices and certain Class I devices.[66] The purpose of the QSR design control requirements is to ensure that the design of a medical device is monitored and controlled such that all specified design requirements are achieved. The phases of design controls[67] include the following:

- Design input: physical and performance requirements of the device for its intended use, including the needs of the user and patient;
- Design output: results of the design effort at each design phase and at the end of design development, including the device, labeling and packaging, associated specifications and drawings, and production and quality assurance specifications and procedures;
- Design review: conduct of formal, documented reviews of design results at appropriate intervals during device design development;
- Design verification: testing to verify the design output meets design input requirements;
- Design validation: (i) testing device performance under actual or simulated conditions of use, in order to establish by objective evidence that device specifications satisfy user needs and intended use(s); (ii) includes risk analysis, where appropriate;
- Design transfer: transition of device design from research and development to production specifications;

[61] 21 CFR § 820.5.
[62] 21 CFR § 820.20(a).
[63] 21 CFR § 820.20(d).
[64] 21 CFR § 820.22.
[65] 21 CFR § 820.25.
[66] 21 CFR 820.30(a).
[67] 21 CFR 820.30(c) through (i).

- Changes in device design: procedures for the identification, documentation, validation or where appropriate verification, review and approval of design changes before implementation.

3. Complaint Files

Device manufacturers are required to establish and maintain procedures for receiving, reviewing, and evaluating complaints. A "complaint" is defined as "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution."[68] Complaint handling procedures must ensure that all complaints are processed in a uniform and timely manner, that oral complaints are documented upon receipt, and that complaints are evaluated to determine whether the complaint represents an event that is required to be reported to FDA as a Medical Device Report. Any complaint that is an MDR-reportable event must be promptly reviewed, evaluated, and investigated.[69] Note that Medical Device Reporting requirements are discussed below in Section II.G.

Notably, all complaints must be reviewed and evaluated to determine if an investigation is necessary. If an investigation is not done, the reason it was not done and the name of the individual responsible for the decision not to investigate must be maintained in the complaint files. Any complaint involving the possible failure of a device, its labeling or packaging to meet specifications must be reviewed, evaluated, and investigated, unless investigation has already been done for a similar complaint and another investigation is not necessary.[70]

G. Manufacturer Serious Adverse Event Reporting Requirements

1. Historical Perspective

Since 1984, domestic manufacturers of medical devices have been required to report to the FDA all device-related deaths, serious injuries, and certain malfunctions. The statutory authority for the Medical Device Reporting (MDR) regulation is Section 519(a) of the Federal Food Drug & Cosmetic Act (FDCA). On September 14, 1984 (49 FR 36326), FDA issued Medical Device Reporting (MDR) regulations for manufacturers and importers under the FDCA and the Medical Device Amendments of 1976 (Public Law 94-295). To correct weaknesses noted in the 1976 amendments and to better protect the public health, Congress enacted the Safe Medical Devices Act of 1990 (SMDA) (Public Law 101-629). SMDA imposed significant new reporting requirements on the medical device industry, including user facilities and distributors of medical devices. To implement SMDA and changes mandated by the Medical Device Amendments of 1992 (Public Law 102-112) (amending certain provisions, Section 519 of the FDCA, relating to reporting of adverse events), FDA published the final MDR regulation for user facilities and manufacturers in the Federal Register on December 11, 1995. The new MDR regulation became effective on July 31, 1996.

[68] 21 CFR § 820.3(b).
[69] 21 CFR § 820.198.
[70] *Id.*

The FDA Modernization Act of 1997 (FDAMA) (Public Law 105-115) was signed on November 21, 1997, and FDAMA changes to medical device adverse event reporting (MDR) became effective on February 19, 1998. On January 26, 2000, changes to the implementing regulations, 21 CFR Parts 803 and 804, were published in the Federal Register to reflect these amendments in the FDCA. Also, Part 804, Medical Device Distributor Reporting, was removed. The MDR Rule changes became effective March 27, 2000.

2. Postmarket Vigilance/Surveillance – Medical Device Reporting (MDR) Regulation: 21 CFR Part 803

The purpose of Medical Device Reporting is to protect the public health by ensuring that devices are not adulterated or misbranded and are safe and effective for their intended use. The MDR regulation provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events in order that safety problems may be detected and corrected in a timely manner. While the requirements of the regulation can be enforced through legal sanctions authorized by the FDCA, accomplishing the objectives of the regulation is dependent on the compliance and cooperation of manufacturers and other affected entities such as user facilities, importers, and distributors.

Reporting device problems to the FDA is a critical communication link to ensure the safety and effectiveness of marketed medical devices. FDA continually evaluates the Manufacturer and User Facility Device Experience Database (MAUDE), which includes reports of adverse events involving medical devices, to detect potential hazards, or safety signals. The sooner the FDA learns about a problem, the sooner the Agency can take action to evaluate actual or potential risk and ensure that any necessary corrective action is initiated to protect patient safety. Sometimes a single report can initiate this action.[71]

2.1 Applicable Definitions

The FDA defines the terms that are used in the MDR regulation. Some of the terms that are significant for purposes of this Report include:

2.1.1 *MDR reportable event (or reportable event)*: An event that user facilities (e.g., hospital, ambulatory surgical facility, outpatient treatment facility) become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury; or an event that manufacturers become aware of that reasonably suggests that one of their marketed devices:

i. May have caused or contributed to a death or serious injury; or
ii. Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

[71] Improving Patient Care by Reporting Problems with Medical Devices. *A MedWatch Continuing Education Article*. Uniformed Services University of the Health Sciences and FDA. September 1997.

2.1.2 *Malfunction* means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in 21 CFR § 801.4.

2.1.3 *Become aware* means that an employee of the manufacturer has acquired information that reasonably suggests a reportable adverse event has occurred.

1) For an event that is required to be reported within 30 calendar days, a manufacturer is considered to have become aware of the event when any of its employees becomes aware of the reportable event.
2) For an event reportable within 5 work days, the manufacturer is considered to have become aware of the event when any of its employees with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or whose duties relate to the collection and reporting of adverse events, becomes aware, from any information, including any trend analysis, that a reportable MDR event or events necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health.

2.1.4 *Reasonably suggests* means any information, including professional, scientific, or medical facts, observations, or opinions, that may reasonably suggest that a device has caused or may have caused or contributed to a MDR reportable event.

2.1.5. *Caused or contributed* means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error.

2.1.6. *Serious injury* means an injury or illness that:

1) Is life-threatening;
2) Results in permanent impairment of a body function or permanent damage to a body structure; or
3) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

2.1.7 *Permanent* means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

2.1.8 "The term '*user error*' means any error made by the person using the device. A user error may be the sole cause or merely contribute to a reportable event. As with the 1984 regulation, there is the requirement for reports of certain adverse device events caused by user error. For example, device injuries attributed to user error may show that the device is misbranded within the meaning of section 502(f) of the FD&C Act [21 U.S.C. 352(f)] in that the

> device fails to bear adequate directions for use or adequate warnings. Reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries. (Refer to the FR preamble, page 63583, Final Rule, December 11, 1995.)"[72]

With these definitions in place, I will now address the manufacturer reporting requirements for the investigation, evaluation and reporting of serious adverse events.

3. Overview of Manufacturer Reporting Requirements

Part 803 of the Code of Federal Regulations Title 21 (21 CFR Part 803) is the implementing regulation for Medical Device Reporting. This Part establishes the requirements for medical device reporting for medical device manufacturers, importers, user facilities, and distributors. Regulations from this Part that are applicable to my analysis and professional opinions herein include the following:

(1) **Deaths and serious injuries that a manufacturer's device has or may have caused or contributed to must be reported to the FDA**;
(2) **Certain device malfunctions must also be reported**;
(3) The device manufacturer is required to establish and maintain adverse event files;
(4) **The device manufacturer is required to submit supplemental/follow-up reports when new (required) information is obtained that was not available when the initial Medical Device Report was submitted to FDA.**

4. Reporting of Adverse Events

A manufacturer is required to investigate, evaluate and submit reports of adverse events to the FDA pursuant to 21 CFR § 803.10(c); § 803.20(a), (b)(3); §803.50(a), (b); §803.52; §803.53; §803.56.

4.1 30-Day Reports

A manufacturer must submit reports of individual adverse events no later than 30 calendar days after the day that the manufacturer becomes aware of information from any source that reasonably suggests that a device may have caused or contributed to a death, serious injury, or a malfunction that, should it recur with the device in question or a similar device, would be likely to cause or contribute to a death or serious injury.[73]

4.2 5-Day Reports

In the case of a reportable event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health, the manufacturer must submit reports of individual adverse events no later than five (5) work days after the day the manufacturer becomes aware of the

[72] Medical Device Reporting for Manufacturers, Prepared by Division of Small Manufacturers Assistance Office of Communication, Education, and Radiation Programs, FDA CDRH, March 1997.
[73] 21 CFR § 803.10(c)(1); § 803.20(b)(3); § 803.50(a).

event. The manufacturer may become aware of the need for remedial action from any information, including any trend analysis.

Additionally, the FDA may make a written request for the submission of a 5-day report. In such case, the manufacturer must submit, without further requests, a 5-day report for all subsequent events of the same nature that involve substantially similar devices for the time period specified in the written request, which time period may be extended if FDA determines it is in the interest of the public health.[74]

4.3 Mandatory Reporting Information Requirements

The manufacturer must submit such mandatory reports using the FDA Form 3500A.[75] On this form, the manufacturer must provide all information required that is reasonably known to the manufacturer.

4.3.1 *Reasonably known* is considered to include the following information:

a) Any information that the manufacturer can obtain by contacting a user facility or other initial reporter;

b) Any information in the manufacturer's possession;

c) Any information that the manufacturer can obtain by analysis, testing, or other evaluation of the device.[76]

4.3.2 The manufacturer is responsible for obtaining and submitting to FDA information that is incomplete or missing from reports submitted by user facilities and other initial reporters.[77]

4.3.3 The manufacturer is responsible for conducting an investigation of each event and evaluating the cause of the event. If the manufacturer cannot submit complete information on a report, it must provide a statement explaining why this information was incomplete and the steps taken to obtain the information.[78]

4.3.4 If the manufacturer later obtains any required information that was not available at the time the initial Medical Device Report was filed, it must submit this information in a supplemental report.[79]

5. When is a Manufacturer Excused from Submitting an MDR?

A manufacturer does not have to report an adverse event if it has information that would lead a person who is qualified to make a medical judgment to reasonably conclude that a device did not cause or contribute to a death or serious injury.[80] Persons qualified to make a medical

[74] 21 CFR § 803.10(c)(2); § 803.20(b)(3); § 803.53.
[75] 21 CFR § 803.20(a).
[76] 21 CFR § 803.50(b)(1).
[77] 21 CFR § 803.50(b)(2).
[78] 21 CFR § 803.50(b)(3).
[79] *Id.*
[80] 21 CFR § 803.20(c)(2).

judgment include physicians, nurses, risk managers, and biomedical engineers. The manufacturer must keep in its MDR event files the information that the qualified person used to determine whether or not a device-related event was reportable.

A manufacturer is not required to submit a Medical Device Report if it determines that the information received is erroneous in that a device-related adverse event did not occur.[81] The manufacturer must retain documentation of such report in its MDR files for the time periods specified below under "Records Retention."[82]

When a manufacturer receives reportable event information for a device it does not manufacture, it is not required to submit a Medical Device Report, but the manufacturer must forward this information to the FDA with a cover letter explaining that it did not manufacture the device in question.[83]

6. The Submission of a MDR is Not an Admission of a Causal or Contributory Relationship

21 CFR § 803.16 makes clear that the manufacturer's submission of a MDR or release of that report by FDA is not necessarily an admission that the device, or the manufacturer or its employees, caused or contributed to the reportable event. The manufacturer does not have to admit and may deny that the report or information submitted under 21 CFR Part 803 constitutes an admission that the device, the manufacturer or its employees, caused or contributed to the reportable event. This regulation underscores the purpose of Medical Device Reporting, even when the manufacturer is in doubt that its device caused or contributed to a reportable event, i.e., to ensure that signals are not overlooked but can be identified and acted upon by the company and the FDA in a timely manner.

7. Requirements for Written MDR Procedures and Recordkeeping

7.1 Standardized Procedures

The manufacturer must develop, maintain, and implement written MDR procedures to identify, communicate, and evaluate adverse events. There must be a standardized review process for determining when an event meets the criteria for reporting under 21 CFR Part 803, and the information must be submitted to the FDA timely. Records must be maintained for all information that was evaluated to determine if an adverse event was reportable, and all Medical Device Reports and information submitted to FDA must be maintained. The company must have systems that ensure timely access to these records for follow-up and inspection by FDA.[84]

[81] 21 CFR § 803.22(b)(1).
[82] 21 CFR § 803.18(c).
[83] 21 CFR § 803.22(b)(2).
[84] 21 CFR § 803.17.

7.2 Establishing and Maintaining MDR Event Files

The manufacturer of a medical device is required to establish and maintain MDR event files. All MDR event files must be clearly identified and maintained to facilitate timely access.[85]

"MDR event files" are written or electronic files and must contain:

1) Information in the manufacturer's possession or references to information related to the adverse event, including all documentation of deliberations and decision-making processes used to determine if a device-related death, serious injury, or malfunction was or was not reportable under 21 CFR Part 803; and
2) Copies of all MDR forms, as required by 21 CFR Part 803, and other information related to the event that the manufacturer submitted to FDA.

A manufacturer may maintain MDR event files as part of its complaint file, under 21 CFR Part 820, if the MDR reportable events are prominently identified as such.

7.3 Records Retention

The medical device manufacturer must retain a MDR event file relating to an adverse event for a period of two (2) years from the date of the event or a period of time equivalent to the expected life of the device, whichever is greater.[86] Accordingly, in the case of a permanently implantable medical device, the regulations require the manufacturer to maintain MDR event files indefinitely.

8. Global Harmonization Task Force (GHTF) Guidances: Postmarket Vigilance

The Global Harmonization Task Force (GHTF)[87] was conceived in 1992 to address the growing need for international harmonization in the regulation of medical devices, with two principal aims: (i) enhancing patient safety and (ii) increasing access to safe, effective, and clinically beneficial medical technologies worldwide. Note that GHTF was disbanded and transitioned its unfinished work to its successor organization in 2012: IMDRF, International Medical Device Regulators Forum. During its approximately 20-year existence, GHTF was a partnership between regulatory authorities and the regulated medical device industry and was comprised of five Founding Members: United States, European Union, Canada, Australia, and Japan. Beginning in 2006, membership expanded to include three Liaison Body members: International Organization for Standardization (ISO), International Electrotechnical Commission (IEC), and Asian Harmonization Working Party (AHWP). A primary purpose of the GHTF was to encourage convergence in regulatory practices related to ensuring the safety as well as the effectiveness/performance and quality of medical devices. This was accomplished through the development and dissemination of harmonized guidance documents concerning basic regulatory practices. These documents were developed by different GHTF

[85] 21 CFR § 803.17.
[86] 21 CFR § 803.18(c).
[87] Global Harmonization Task Force Website: http://www.ghtf.org/.

Study Groups and provide a model for the regulation of medical devices and adoption/implementation by national regulatory authorities.

The GHTF Study Group 2 (SG2) was responsible for developing guidance documents concerning medical device vigilance such as medical device reporting and postmarket surveillance. Specifically, SG2 was charged first with reviewing current adverse event reporting, postmarket surveillance and other forms of vigilance for medical devices and performing an analysis of different requirements amongst countries with developed device regulatory systems and then using this information to develop harmonized guidances for data collection and reporting systems. A number of the finalized SG2 guidance documents provide medical device industry standards of practice applicable to the subject matter of this Report, e.g.: (i) Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative;[88] (ii) Manufacturer's Trend Reporting of Adverse Events;[89] and (iii) Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices.[90]

Timothy A. Ulatowski, former Director, Office of Compliance, Center for Devices and Radiological Health (CDRH), U.S. Food and Drug Administration, advised device manufacturers at the 2009 AAMI/FDA Conference on Medical Device Standards and Regulation to keep apprised of the GHTF, as its new standards and guidance documents could influence FDA regulation, stating that "Companies need to become more aware because we're all moving in this direction…GHTF is becoming the global nomenclature."[91]

9. Underreporting of Adverse Events

The FDA relies on the MedWatch postmarketing surveillance program to monitor drug (and biologics) adverse reactions through a database known as the FDA Adverse Event Reporting System (FAERS) and the MAUDE database for Medical Device Reporting. Despite these mandatory and voluntary reporting programs, postmarket adverse event underreporting is pervasive throughout the system. The FDA recognizes that only a small percentage of the total burden of adverse events is captured through MedWatch and "generally assumes that only 1 in 10 adverse (drug) events is reported."[92] Although device-related adverse events are at least as common as drug-related events in the hospital, in-hospital device use and device-related problems are poorly documented.[93, 94] This vast under-recognition of device-related

[88] GHTF FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative. June 29, 1999.
[89] GHTF FINAL DOCUMENT: Manufacturer's Trend Reporting of Adverse Events. January 2003.
[90] GHTF FINAL DOCUMENT: Medical Devices Post Market Surveillance: Global Guidance for Adverse Event Reporting for Medical Devices. November 30, 2006.
[91] Ulatowski: GHTF to Guide FDA Regulations, Guidances. *The QMN Weekly Bulletin.* April 17, 2009; Vol 1 No 16.
[92] Drazen JM et al. Current adverse event reporting systems. Adverse Drug Event Reporting: The Roles of Consumers and Health-Care Professionals: Workshop Summary, Forum on Drug Discovery, Development, and Translation. *National Academy of Sciences* 2007.
[93] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.

problems may help to explain why the rate of postmarket adverse event reporting is even bleaker for medical devices, with congressional reports estimating that as few as 1 in 100 medical device reportable events are actually reported.[95] Bright and Shen estimated that, at the national level, 14% of adverse medical device effects were reported to CDRH in 2003. However, since this estimate was based on hospital discharge records, the true rate of underreporting for this population is unknown but certainly less than 14%.[96] Reasons for underreporting of adverse events include, among others, that healthcare providers may be too busy or fail to see that reporting would be useful, may be unaware of the FDA medical device adverse event reporting program, or fear blame for the medical device adverse event.[97]

H. Recalls

FDA defines "recall" as a "firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure."[98] "Removal means the physical removal of a device from its point of use to some other location for repair, modification, adjustment, relabeling, destruction, or inspection."[99] A "correction" is defined as "the repair, modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a device without its physical removal from its point of use to some other location."[100,101]

Recalls may be initiated by a medical device manufacturer, or they may be conducted by the manufacturer at FDA's request or by FDA order under statutory authority.[102] Recalls initiated by the manufacturer or conducted upon FDA's request are considered voluntary recalls. Those conducted in response to FDA order are mandatory recalls. In practice, almost all medical device recalls are voluntary.

A manufacturer's decision to conduct a voluntary recall is based on a determination that the product is violative under the FDCA and that the FDA would be likely to initiate legal action. In making such determination, the manufacturer should consider if a violation of the adulteration and misbranding provisions of the FDCA exists. Under 21 CFR Part 7, a field correction can be done as appropriate if a manufacturer determines a recall is necessary. To continue the marketing and sale of violative product may constitute prohibited acts under the FDCA.

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[94] Samore MH et al. Surveillance of medical device-related hazards and adverse events in hospitalized patients. *JAMA* 2004;291:325-334.
[95] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological aspects of postmarket medical device safety, estimates of the frequency of adverse medical device events, lack of documentation in healthcare records of device use and device-related problems, underreporting of adverse medical device events.
[96] Bright RA and Shen J. Use of a free, publicly-accessible data source to estimate hospitalizations related to adverse medical device events. Draft manuscript, 2005.
[97] Ensuring the Safety of Marketed Devices. CDRH's Medical Device Postmarket Safety Program. Jan. 18, 2006. Appendix B, Epidemiological Aspects of Postmarket Medical Device Safety.
[98] 21 CFR § 7.3(g).
[99] 21 CFR 806.2(i).
[100] 21 CFR 806.2(d).
[101] 21 CFR § 7.3(h).
[102] FDCA § 518, 21 U.S.C. § 360h.

III. CLINICAL BACKGROUND: STRESS URINARY INCONTINENCE (SUI)

A. SUI Overview

Incontinence occurs when the normal relationship between the lower urinary tract components (bladder, urethra and sphincter, pelvic floor and the nervous system) is disrupted, resulting from nerve damage or direct mechanical trauma to the pelvic organs. Advancing age, higher parity, vaginal delivery, obesity and menopause are associated with an increase in risk. There are different types of urinary incontinence. Stress incontinence (SUI) is the symptom of involuntary loss of urine during situations of increased intra-abdominal pressure, such as coughing or sneezing. Obesity and smoking are also risk factors for SUI.[103] Two types of stress incontinence are recognized, one from a hypermobile but otherwise healthy urethra and one from deficiency of the sphincter itself. Urethral hypermobility is a manifestation of weakened support of the proximal urethra while sphincter deficiency is an indication of compromised ability of the urethra to act as a watertight outlet. There is no standardized test to differentiate between them accurately, and there is increasing belief that both types are present most of the time although to differing degrees. Urge incontinence is the symptom of involuntary loss of urine associated with a sudden, strong desire to void (urgency). It is usually a manifestation of uncontrolled bladder wall contraction (detrusor overactivity). Mixed incontinence is the condition of urine leakage with features of both stress and urgency.

Conservative therapy, with or without the use of medications, is generally undertaken before resorting to surgery. Examples of nonsurgical treatment options for SUI include:

- Pelvic Floor Exercises: A type of exercise to strengthen the pelvic floor by contracting and relaxing the muscles that surround the opening of the urethra, vagina, and rectum. These exercises, commonly referred to as Kegel exercises, improve the muscles' strength and function and may help to hold urine in the bladder longer.
- Pessary: A removable device that is inserted into the vagina against the vaginal wall and urethra to support the bladder neck. This helps reposition the urethra to reduce SUI.
- Transurethral Bulking Agents: Collagen injections around the urethra that make the space around the urethra thicker, thus helping to control urine leakage. The effects may not be permanent.
- Behavioral Modification: This includes avoiding activities that trigger episodes of leaking.

Surgery to decrease or prevent urine leakage can be done through the vagina or abdomen. The urethra or bladder neck is supported with either stitches alone or with tissue surgically removed from other parts of the body such as the abdominal wall or leg (fascial sling), with tissue from another person (donor tissue) or with material such as surgical mesh (mesh sling). Surgical mesh in the form of a "sling" (sometimes called "tape") is permanently implanted to support the urethra or bladder neck in order to correct SUI. This is commonly referred to as a "sling procedure." The use of surgical mesh slings to treat SUI provides a less invasive approach than

[103] Medical Devices: Stress Urinary Incontinence (SUI), http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/UroGynSurgicalMesh/ucm284109.htm

non-mesh repairs, which require a larger incision in the abdominal wall. The multi-incision sling procedure can be performed using three incisions, in two ways: with one vaginal incision and two lower abdominal incisions, called retropubic or TVT; or with one vaginal incision and two groin/thigh incisions, called transobturator (TVT-O). There was also a "mini-sling" procedure that utilized a shorter piece of surgical mesh, which could be done with only one incision.

The number of women who undergo surgery for SUI has increased significantly over the last three decades, both for overall and age-adjusted procedures.[104,105] From January 1979 to December 2004, a cross-sectional study was performed in which data abstracted from the National Hospital Discharge Survey (NHDS) showed that approximately 2,064,940 SUI surgeries were performed in the US.[7] In 1979 (prior to the introduction of the TVT procedure), 48,345 surgeries were performed, compared to 103,467 in 2004. Rates of incontinence surgeries increased by 1.4% per year overall and 4.4% per year in women ≥52 years of age. Retropubic urethral suspension procedures such as the Burch colposuspension decreased over the time period. Suburethral sling procedures increased from 1,591 in 1979 to a peak of 10,212 in 1997, then decreased to 4,314 in 2004. The decreases seen with traditional retropubic and suburethral sling procedures may be due to the increase in use of midurethral sling procedures, which did not have a separate code in the NHDS database and were therefore likely coded as "Other." Another weakness of this study was that outpatient procedures, which are becoming increasingly common, were not captured. In a study using the Nationwide Inpatient Sample and the National Survey of Ambulatory Surgery, the number of women who underwent surgery for SUI during 2006-2007 was calculated.[8]

Success rates for non-sling (i.e., open abdominal retropubic suspension) and TVT are generally considered to be equivalent and are in the order of 68.9% to 88%, although lower rates have also been cited.[106] A recent overview of complications associated with sling procedures was published by Ortega-Castillo and Neri-Ruiz.[107] Intraoperative complications included bladder perforation (rates ranging from 0% [TVT-O only] to 25% in different studies), nerve lesion (rare), and bleeding, including cases of vascular injury (rates ranging from 0.1% to 2.5%) Surgical experience accounts for at least some of the variability in intraoperative complication rates. Immediate post-surgical complications included hematoma, voiding disorders and infection. Hematomas may resolve spontaneously or require intervention such as drainage (minimally invasive) or laparotomy. Voiding disorders (urinary retention, difficulty in voiding) often are short-lived and most can be managed by intermittent catheterization for a period of days. In some cases, the sling may need to be released or cut. Infection may be managed by antibiotic treatment or, in extreme cases, debridement or even colostomy. Some patients may

[104] Oliphant SS, Wang L, Bunker CH, Lowder JL. Trends in stress urinary incontinence inpatient procedures in the United States, 1979-2004. Am J Obstet Gynecol 2009;200:521e1-521-e6.
[105] Wu JM, Kawasaki A, Hundley AF, Dieter AA, Myers ER, Sung VW. Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. Am J Obstet Gynecol 2011;205:230e1-230e5.
[106] Lapitan MCM, Cody JD. Open retropubic colposuspension for urinary incontinence in women (Review). 2012 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.; Ward et al. A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: Two-year follow-up. American Journal of Obstetrics and Gynecology (2004) 190, 324-31; Ward et al., Tension-free vaginal tape versus colposuspension for primary stress incontinence 5-year follow up, *BJOG*, 2008.
[107] Ortega-Castillo V, Neri-Ruiz ES. Surgical complications with synthetic materials, Urinary Incontinence. Alhasso A, ed. InTech, 2012. http://www.intechopen.com/books/urinary-incontinence/complications-of-genital-prolapse-and-urinaryincontinence-surgery

develop a chronic infection causing symptoms years after sling placement. Late complications include de novo urgency, voiding disorders, pain and suprapubic discomfort, mesh erosion/extrusion, intestinal lesion, nerve lesion and dyspareunia.

B. Food and Drug Administration Search of the MAUDE Database

In 2011, FDA convened an Obstetrics & Gynecology Devices Advisory Committee Meeting to discuss the use of surgical mesh for treatment of pelvic organ prolapse (POP) and SUI. As part of their presentation, FDA presented an executive summary that included results of searches of the MAUDE database. Data from the search covering the 2008-2010 timeframe are presented here because FDA presented POP and SUI complications separately. This search identified 2,874 MDRs for urogynecologic surgical mesh, with slightly less than half associated with SUI repairs; notably, these MDRs were additional to the 1,000 that the Agency had identified previously in its 2008 search of the MAUDE database for the years 2005-2007. Adverse events associated with SUI sling procedures included pain, mesh erosion, infection, urinary problems, organ perforation, incontinence recurrence, bleeding, dyspareunia, neuromuscular problems and vaginal scarring. (Please also reference Section IX. for additional information.)

IV. REGULATORY HISTORY: ETHICON'S SURGICAL AND TRANSVAGINAL MESH PRODUCTS

A. Methodology Used and Construction of Regulatory History

To review and evaluate the overall regulatory history of Ethicon's surgical mesh products, a simple search of FDA's searchable 510(k) database was conducted for the following terms:

- Ethicon
- Surgical mesh
- Gynecare
- Product code FTL
- Product code OTN
- TVT
- Johnson & Johnson (J&J)
- Boston Scientific

The J&J simple search was further refined using an "advanced search" for the following parameters:

- J&J, surgical mesh; 1 Jan 1998 to the present
- Ethicon, surgical mesh; 1 Jan 1998 to the present

The result of these searches is presented in Tables IV.1, IV.2, IV.3, and IV.4 and provides a hierarchic representation of the product development and predicate history that eventuated in the marketing of the GYNECARE Tension Free Vaginal Tape (TVT) System. For each mesh product presented, the 510(k)-cleared indications for use, the 510(k) number, the date FDA received the 510(k), the date FDA cleared the device for marketing [510(k)-clearance], and predicate information are provided.

Additionally, I reviewed the 510(k) applications and associated documentation from Ethicon's 510(k) files of particular relevance to the subject matter of this Report and reviewed deposition testimony in which 510(k) submissions and the regulatory process were discussed. Key information pertinent to an understanding of the development and regulatory history of the TVT product is presented in the following section.

B. Overview: Development and Regulatory History of Ethicon's Surgical and Transvaginal Mesh Products

PROLENE nonabsorbable polypropylene suture, the first of Ethicon's surgical mesh product line, was initially regulated as a drug and approved by NDA 16374 prior to the enactment of the Medical Device Amendments (MDA) on May 28, 1976. Following passage of the MDA, devices that had been regulated previously as new drugs and approved under New Drug Applications (NDAs) were officially given device status as "transitional devices." A Premarket Approval application (PMA) number with "N" before the application number (which is the original NDA number) denotes a transitional device; the PMA Number for PROLENE is PMA N16374. (The original approval could not be located through online search efforts that included a search of the FDA PMA database, a general search of CDRH, a search of "drugs @ FDA" for approved drug products, and a "Google" search. However, a listing of the supplements to this PMA was found, with a December 31, 1980, decision date for Supplement 001.)

Reclassification as a polypropylene nonabsorbable surgical suture class II device (21 CFR 878.5010), for use in general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures, was published in the Federal Register on May 31, 1991 (Volume 56, No. 105, Pages 24684-24685). This product is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart E, Surgical Devices, Nonabsorbable Polypropylene Surgical Suture. Also in 1991, PROLENE Polypropylene Mesh Plug W/onlay patch was cleared (510(k) Number K915774) under classification regulation 878.3300: surgical mesh defined as metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples are for hernia repair, acetabular and cement restrictor mesh used during orthopedic surgery. This product also is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart D, Prosthetic Devices, Surgical Mesh. All the remaining products discussed in this review were 510(k)-cleared under the classification regulation 21 CFR 878.3300.

The first of 13 Ethicon 510(k)s that could be identified from the 510(k) searchable database for the repair of hernia defects was submitted to FDA in 1996 and was a modification of the PROLENE Polypropylene nonabsorbable synthetic surgical mesh. According to the 510(k) Summary of Safety and Effectiveness, the modified device has the same technological characteristics as the predicate device (i.e., no change in chemistry, material or composition),

but differs from the predicate device in the additional sizes supplied and a precut key hole shape provided as a convenience to the surgeon.[108]

The first of seven 510(k)s (discussed further below) for GYNECARE Tension-free Vaginal Tape (TVT) System and its various line extension devices was granted 510(k)-clearance in 1998 (510(k) Number K974098). This product, the TVT retropubic device which is the subject of this Report, is a pubourethral sling for the treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT device is composed of PROLENE polypropylene mesh (tape), and the mesh is covered with a polyethylene sheath with a slit in the middle.[109]

In 2000, PROLENE Soft Polypropylene Mesh, which is knitted by a process which interlinks each fiber junction, allegedly provided for elasticity in both directionsand is claimed to be 50% more flexible than PROLENE, according to the description in the 510(k) Summary of Safety and Effectiveness,[110] was granted 510(k)-clearance (510(k) Number K001122) based on substantial equivalence to Ethicon's PROLENE (Polypropylene) and MERSILENE Meshes (Ethicon polyester mesh). All three of these products, i.e., PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh and Mersilene Mesh, served as the predicates for the January 2002 GYNEMESH PROLENE Soft (Polypropylene) Mesh 510(k)-clearance for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect. (Emphasis added.)

Table IV.1 Ethicon Surgical Mesh Regulatory History – Other Indications for Use (i.e., not for hernia, stress urinary incontinence, or pelvic floor repair)

510(k) History: Regulation 878.3300

510k #/ date FDA rcvd/ date cleared	Name	Predicate	Indications for use
K915774 12/24/91 03/02/92	PROLENE Polypropylene Mesh Plug W/onlay patch	Unavailable	Unavailable

[108] FDA 510(k) Searchable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K962530.pdf.
[109] FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K974098.pdf.
[110] FDA 510(k) Searchable Database: K001122 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K001122.pdf.

510(k) History: Regulation 878.5010

510k #/ date FDA rcvd/ date cleared	Name	Predicate	Indications for use
K001625 5/17/00 7/10/00	Pronova Nonabsorbale suture	Surgilene and PROLENE sutures	In general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures.

Table IV.2 Ethicon Surgical Mesh Regulatory History – 510(k) History: Hernia Repair: Regulation 878.3300

510k # date FDA rcvd/ date cleared	**Name**	**Predicate**	**Indication/intended use**
K962530 6/28/96 8/9/96	Modified PROLENE Polypropylene mesh nonabsorbable synthetic surgical mesh	PROLENE polypropylene mesh nonabsorbable synthetic surgical mesh	Repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material.
K972412 6/26/97 9/10/97	PROLENE Polypropylene Mesh Hernia Device Nonabsorbable Synthetic Surgical Mesh Implant	Bard® Marlex® Mesh Perfix® Plug Nonabsorbable Polyproylene surgical mesh device	Repair of inguinal hernia defects, both indirect and direct.
K984220 11/25/98 2/23/99	Modification: PROLENE(Polypropylene) Hernia System	(Polypropylene) Hernia System	Repair of abdominal wall hernia defects.
K001122 4/7/00 5/23/00	PROLENE Soft (Polypropylene) Mesh	PROLENE (Polypropylene) Mesh and Mersilene Mesh	Repair of hernia or other fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result.

Table IV.3 Ethicon Surgical Mesh Regulatory History – 510(k) History: Pelvic Floor Repair: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication/intended use
K013718 11/8/01 1/8/02	Gynemesh PROLENE Soft (Polypropylene) Mesh	PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh, and MERSILENE Mesh	Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect

Table IV.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300

510k # date FDA rcvd/ date cleared	Name	Predicate[a]	Indication(s) or Intended Use
K963226 08/12/1996 11/15/1996	ProteGen Sling Cleared under device name "Surgical Fabrics"	K945377 Trelex Natural Mesh K961810 Supple Peri-Guard K930822 Gore-Tex Soft Tissue Patch Marlex Mesh Mersilene Mesh	Intended to reinforce soft tissue where weakness exists for the urological, gynecological and gastroenterological anatomy inclusive but not limited to the following procedures: pubourethral support, urethral and vaginal prolapse repair, colon and rectal prolapse repair, reconstruction of the pelvic floor, bladder support, and sacro-colposuspension.
K974098 10/30/97 1/28/98	Gynecare TVT Tension-free Vaginal Tape	K963226 ProteGen Sling Collagen Impregnated Material	As a pubourethral sling indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate the placement of the TVT device.

Table IV.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K012628 8/13/01 10/26/01	TVT System with three accessories (modification)	K974098 Gynecare Tension Free Vaginal Tape (TVT) System with Accessories: TVT reusable introducer TVT reusable rigid catheter guide Cook OB/GYN Stamey Needle	Same (As a pubourethral sling indicated for treatment of stress urinary incontinence, for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT Introducer and Rigid Catheter Guide accessories are intended to facilitate placement of the TVT device.)
K033568 11/13/03 12/8/03	Gynecare TVT Obturator Device	K974098 and/or K012628 (not specified in available documentation) Gynecare TVT Device	For the treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.
K052401 9/1/05 11/28/05	Gynecare TVT Secur System	K974098 and K012628 Gynecare TVT System K033568 Gynecare TVT Obturator	For the treatment of stress urinary incontinence (SUI), for female urinary incontinence resulting from urethral hypermobility and/or intrinsic sphincter deficiency.
K100485 2/19/10 3/16/10	Gynecare TVT Exact Continence System	K974098 Gynecare TVT Tension Free Vaginal Tape	As a pubourethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.

Table IV.4 Ethicon 510(k) History : Gynecare TVT: Regulation 878.3300 (contd.)

510k # date FDA rcvd/ date cleared	Name	Predicate	Indication
K100936 4/5/10 7/1/10	Gynecare TVT Abbrevo Continence System	K033568 Gynecare TVT Obturator System	Same (As a pubourethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.)
K132054 07/09/2013 08/23/2013	Gynecare TVT Exact Continence System	K100485 Gynecare TVT Exact Continence System	Same (As a pubourethral sling for treatment of female Stress Urinary Incontinence, resulting from urethral hypermobility and/or intrinsic sphincter deficiency.)
[a] Predicate names are reproduced as written in the Summaries of Safety and Effectiveness and may therefore not match exactly between 510(k)s.			

V. REGULATORY HISTORY: GYNECARE TVT™ RETROPUBIC SYSTEM AND LINE EXTENSION FAMILY OF PRODUCTS

A. Methodology Used and Construction of Relevant History

To review the regulatory history specific to the Gynecare TVT Retropubic System (TVT or TVT Classic), the subject of this Report, I principally looked at 510(k) applications, the documentation in Ethicon's 510(k) and related files, and the FDA's searchable 510(k) database. Additionally, I reviewed deposition testimony in which the regulatory process was discussed in some detail. The 510(k) clearance for TVT, including the 510(k)-cleared indications for use, the 510(k) number, the date FDA received the 510(k), and the date FDA cleared the device for marketing (510(k)-clearance) are provided above in Table IV.4. Also shown in Table IV.4 are the line extension products in the TVT family of products.

B. Overview: Regulatory History of Ethicon's TVT Slings for Stress Urinary Incontinence

The first preconfigured sling product cleared for use was the ProteGen Sling in 1996, manufactured by Boston Scientific Corporation (K963226).[111] The ProteGen sling was a woven polyester mesh impregnated with bovine collagen. Among its intended uses was "pubourethral support." Boston Scientific cited five predicates for the ProteGen Sling. Two of the predicates were constructed of polypropylene (Trelex Natural Mesh, Marlex Mesh), one was a polyester mesh (Mersilene Mesh, a pre-amendment device), one was bovine pericardium cross-linked with glutaraldehyde (Supple

[111] FDA 510(k) Releasable Database: K963226 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K963226.pdf

Peri-Guard), and one was polytetrafluoroethylene (Gore-Tex Soft Tissue Patch). Only Supple Peri-Guard has a 510(k) summary available in the FDA's releasable 510(k) database. The Protegen Sling was withdrawn from the market by Boston Scientific in January 1999 due to complaints of mesh complications, including discomfort, dyspareunia, and mesh erosion.[112] The FDA found that the product was "misbranded and adulterated" and did "not appear to function as intended."[113]

Ethicon's first TVT sling was the Gynecare Tension-Free Vaginal Tape System. Ethicon entered into an agreement on February 14, 1997, with Medscand, the company that Pr. U. Ulmsten, a Swedish surgeon who developed the TVT procedure, relied upon to obtain prototypes for clinical use and that had applied for a patent.[114] Ethicon submitted the 510(k) for the TVT System to FDA on October 30, 1997, and received clearance to market on January 28, 1998 (K974098).[115] The ProteGen sling was the predicate device. The Gynecare TVT (Retropubic) System is comprised of a polypropylene (Prolene) mesh tape covered with a polyethylene sheath, a stainless steel TVT Introducer to facilitate passage of the tape from the vagina to the abdominal skin, and a TVT Rigid Catheter Guide that adds rigidity to the Foley catheter during surgery. According to the Summary of Safety and Effectiveness, the Ethicon TVT was the same **technologically** as the predicate; i.e., "**both are meshes that provide pubourethral support**". Further, "**Any differences between the two devices do not raise new questions of safety and effectiveness.**" [Emphasis added.]

In their 510(k) submission, Ethicon presented data from three clinical trials.[116] The first was an abstract containing preliminary data by Wang and Lo (undated). In this study, 70 women were treatedfor SUI according to the Ulmsten procedure. Follow-up was from 3-12 months. Three bladder perforations were reported and 11/70 patients had blood loss > 200mL requiring an indwelling catheter and vaginal tamponade. No defects in healing healing or tape rejection were reported. The second was the 1996 Ulmsten paper that described the original procedure performed by Pr. Ulmsten.The third was an ongoing Scandinavian multicenter study that had preliminary data from 131 patients implanted with the intravaginal slingplasty (IVS) device. Only early postoperative complications were presented. In the Ulmsten study, five patients experienced delayed voiding requiring an indwelling catheter for the first night after surgery, and five patients developed a urinary tract infection that resolved with antibiotic treatment. No instances of tape rejection or defect in healing were reported. In the Scandinavian study, delayed voiding occurred in four patients, three of whom required catheterization from one to three days; the fourth required intervention. There was one case of a bladder perforation, one hematoma, and one case of vaginal infection requiring resection of exposed mesh. .

It should be noted that all of the clinical data support (as set forth above) submitted by Ethicon in support of the 510(k) for the TVT was data from small studies that utilized the IVS device, not the actual TVT device. It is appears from the testimony in this case that the IVS device was different

[112] Nussbaum A, et al. J&J Mesh Approved by FDA Based on Recalled Device. Bloomberg article (2011). http://mobile.bloomberg.com/news/2011-10-20/j-j-vaginal-mesh-approved-by-fda-based-on-older-recalled-device

[113] Cohen R, et al. A surefire profit-maker could cost its maker dearly. The Star-Ledger (2002). http://www.nj.com/specialprojects/index.ssf?/specialprojects/implants/implantsside2.html

[114] ETH.MESH.03932912 at 913-914: The history of TVT by A. Arnaud, MD, July 12, 2000. It should be noted that Pr. Ulmsten was a shareholder of Medscand. ETH.MESH.09748308: Project TOMEL Due Diligence Summary.

[115] FDA 510(k) Releasable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K962530.pdf

[116] Ethicon Tension-free vaginal tape (TVT) System 510(k) notification. Exhibit No. 415.

from the TVT device in several respects although, admittedly, Ethicon's employees' testimony in this regard is unclear as to exactly what the differences between the devices are. For instance, Laura Angelini, Ethicon's marketing manager in Europe[117] at the time of the launch of the TVT, testified that the mesh used in the TVT was different than the IVS mesh.[118] Axel Arnaud, Ethicon's Medical Director in Europe at the time of the TVT launch, testified that there were differences between the devices including differences in the connection between the mesh and the needles and that the needles were different.[119] Regardless of the differences, the FDA should have been told that the clinical data used to support the TVT submission was developed in studies with different devices.

In addition, Ethicon should have disclosed to the FDA that the studies submitted to support the TVT were performed by investigators (including Pr. Ulmsten) with significant conflicts of interest and, further, that Ethicon paid Medscand $400,000 for the multicenter Scandinavian study only because the study resulted in "favorable results."[120] Professor Ulmsten and Medscand were paid millions by Ethicon, and they were the ones responsible for data from the studies. The FDA should have been told that was the case.

VI. KNOWN HOST RESPONSES AND COMPLICATIONS ASSOCIATED WITH POLYPROPYLENE AND SYNTHETIC MESH

A. Polypropylene (PP) Not Biologically Inert: Inflammatory/ Foreign-Body Responses to PP

Although synthetic materials often are referred to as chemically or physically inert, none is truly biologically inert.[121] Synthetic materials such as polypropylene are known to induce an acute inflammatory response, followed by chronic inflammatory reaction, which elicits a foreign-body response characterized by formation of granulation tissue and fibrosis. The nature of the implant material, including chemical and physical structure, amount of material and surface of the contact area with the patient's tissue, filament and pore size, determines the extent of the inflammatory reaction as well as further tissue in-growth. Other factors, such as material degradation, also may influence inflammatory activity. While the inflammatory phases are necessary for the desired fibrosis process, they may be the source of adverse effects, including implant shrinkage, erosion, and adhesion formation.[122]

Mesh was known to cause an inflammatory response and be subject to shrinkage by the time of TVT launch in 1998. A study in dogs showed that meshes could shrink by 30% (Soft Hernia Mesh multifilament) to 50% (Marlex monofilament) as little as four weeks after implantation.[123] The

[117] Laura Angelini Deposition, September 16, 2013, 18:6-25.
[118] Laura Angelini Deposition, September 16, 2013, 184:4 to 186:10
[119] Axel Arnaud Deposition, July 20, 2013, 521:2-522:20; 462:15-465:17; 503:8-503:19
[120] Laura Angelini Deposition, September 16, 2013, 101:6-110:2; 111:19-112:7; 124:12-15; ETH.MESH.09746948: License and Supply Agreement between Johnson & Johnson International and Medscand Medical A.B.
[121] Deprest J et al. The biology behind fascial defects and the use of implants in pelvic organ prolapse repair. Int Urogynecol J 2006;17:S16-S25.
[122] Deprest J et al. The biology behind fascial defects and the use of implants in pelvic organ prolapse repair. Int Urogynecol J 2006;17:S16-S25.
[123] Klinge U, Klosterhalfen B, Muller M, Ottinger AP, Schumpelick V. Shrinking of polypropylene mesh in vivo: an

amount of mesh contraction correlates with the degree of inflammation and scar formation. Histological analysis showed that both types of meshes induced an inflammatory response, but it was less for the multifilament mesh containing less polypropylene than for the monofilament mesh.[124] The following year, the same group published a study of the inflammatory response to explanted meshes used to repair hernias in humans.[125] Various types of mesh were included in the study (1 polyester, 10 polypropylene, 2 reduced polypropylene, 4 polytetrafluorethylene (PTFE), and 1 absorbable polyglactin). Some of the meshes had been inside the body for years. The partial volume of inflammatory cells varied among the types of meshes tested: polypropylene 32%; PTFE 12%; polyester 8%; and reduced polypropylene 7%. The authors concluded that inflammation induced by the use of alloplastic (synthetic) materials can persist for many years.

The biocompatibility (or bioincompatibility) of synthetic implants is thought to be responsible for various complications of mesh implantation. Three types of mesh materials used for hernia repairs were studied in a rat implantation model: polypropylene (Prolene), polyethylene terephthalate (PET, Mersilene) and polypropylene/polyglactin (PP+PG, Vypro).[126] Histochemical analysis of the inflammatory response was performed at 7 and 90 days after implantation. In all groups, a persisting T-cell response was observed. Colonization of the interface with macrophages showed a pronounced reduction in the PP+PG-mesh group. Infiltration of mast cells at the tissue graft interface showed a time-dependent decrease in the PET- and PP+PG-mesh groups, whereas in contrast, index of mast cells increased in the PP-mesh group. At both time points, indices of proliferation were highest in the PP-mesh group. The authors concluded that these data confirmed the development of biomaterial-dependent chronic inflammatory response to surgical meshes and urged further research on the recruitment of inflammatory cells. Notably, the TVT mesh is "prepared from the same raw material used in the manufacture of PROLENE polypropylene suture."[127] The TVT mesh is PROLENE polypropylene mesh "constructed of knitted filaments of extruded polypropylene strands identical in composition to that used in PROLENE polypropylene nonabsorbable surgical suture."[128]

A study of explanted polypropylene hernia meshes was performed in an attempt to explain pain and recurrences experienced after hernia repair and the results were published in 2007.[129] The objective of the study was to determine whether oxidation plays a role in the degradation of polypropylene mesh in vivo. After implantation of mesh, the body mounts a prolonged inflammatory response, in which phagocytic cells are continually recruited to the site via a process involving oxygen metabolism and release of superoxide radicals and strong oxidants such as hydrogen peroxide and hypochlorous acid. As a result, the mesh material is exposed to a continuous bath of oxidants. In

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experimental study in dogs. Eur J Surg 1998;164(12):965-969. Abstract only.

[124] Klinge U, Klosterhalfen B, Muller M, Ottinger AP, Schumpelick V. Shrinking of polypropylene mesh in vivo: an experimental study in dogs. Eur J Surg 1998;164(12):965-969. Abstract only.

[125] Klinge U, Klosterhalfen B, Muller M, Schumpelick V. Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J surg 1999;165(7):665-673. Abstract only.

[126] Rosch R, Junge K, Schachtrupp A, Klinge U, Klosterhalfen B, Schumpelick V. Mesh implants in hernia repair. Inflammatory cell response in a rat model. Eur J Surg 2003;35(3):161-166. Abstract only.

[127] 510(k) Number K974098: Biocompatibility Testing Results, page 40.

[128] 510(k) Number K974098, Updated Package Insert, submitted January 21 1998, in response to FDA fax request (no Bates number).

[129] Costello CR, Bachman SL, Ramshaw BJ, Grant SA. Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Res Part B:Appl Biomater 2007;83B: 44–49.

this study, the authors characterized 14 hernia mesh explants removed from patients due to complications requiring surgery. Samples were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), thermogravimetric analyis (TGA) and compliance testing. SEM showed cracks and fissures in explanted meshes that were not present in control material. DSC also showed changes from control mesh, indicating that oxidation may have occurred; however, not all of the results were statistically significant. TGA (commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation, or loss of volatiles) showed that most of the explanted samples had experienced weight loss in vivo. Compliance testing showed reduced compliance in all but one sample, which is also evidence of oxidation. The authors concluded that oxidation was the most likely cause of in vivo degradation of polypropylene mesh.

A prospective study in 2009 evaluated the inflammatory response to macroporous monofilament polypropylene mesh after surgery for pelvic organ prolapse in 10 patients.[130] Eight patients served as controls (no mesh implanted). Vaginal punch biopsies were performed presurgery and at 1-year post surgery. Foreign body response to the mesh was assessed using a combination of histological, semiquantitative and computerized image-based analysis. Compared to preoperative histology, there was a significant postoperative increase in macrophage and mast cell counts but no significant changes in the count of cells involved primarily in the infectious cell response or collagen density and the elastin fraction at the mesh-tissue interface. Three cases of mild granuloma formation and two cases of mild erosion were observed. There was no significant change in epithelial thickness. The authors concluded that macroporous monofilament mesh induces a mild but persistent foreign body reaction.

The earliest reports that polypropylene could degrade within the human body were published in the 1980s. A review of various plastic materials used in the manufacture of intraocular lenses was published in 1984.[131] The authors concluded that, whereas polypropylene is a highly effective, relatively inert material, there exists evidence that long-term alterations can occur. Two publications in 1986 reported that cracks had developed in polypropylene suture used intracamerally in intraocular surgery.[132,133] In one of these studies, part of the surface layer of the suture was nearly detached or completely missing, and the diameter had decreased by over 50%.

Clave, et al. studied polypropylene and polyester meshes that had been explanted from patients after complications (erosion, infection and/or shrinkage).[134] All explants were either polypropylene or polyester. One hundred (100) explants were studied histologically, by SEM and by chemical analysis. The authors found that polypropylene mesh is altered in vivo, and low density

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[130] Elmer C, Blomgren B, Falconer C, Zhang A, Altman D. Histological inflammatory responses to transvaginal polypropylene mesh for pelvic reconstructive surgery. U Urol 2009;181(3):1189-1195. Abstract only.

[131] Apple DJ, Mamalis N, Brady SE, Loftfield K, Kavka-Van Norman D, Olson RJ. Biocompatibility of implant materials: a review and scanning electron microscopic study. J Am Intraocul Implant Soc 1984;10(1):53-66. Abstract only.

[132] Altman AJ, Gorn RA, Craft J, Albert DM. The breakdown of polypropylene in the human eye: is it clinically significant? Ann Ophthalmol 1986;18(5):182-185. Abstract only.

[133] Jongebloed WL, Worst JF. Degradation of polypropylene in the human eye: a SEM study. Doc Ophthalmol 1986;64(1):143-152. Abstract only.

[134] Clave A, Yahi H, Hammou J-C, Montanari S, Gounon P, Clave H. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010;21:261-270.

monofilament mesh was less damaged than nonwoven, nonknitted polypropylene. Polyester mesh suffered the least damage. More degradation was observed in the presence of acute infection or chronic inflammation. The authors concluded that their results question the opinion that polypropylene is an inert substance.

A similar conclusion was reached by Dr. Alex Wang, Chang Gung University Hospital, Taiwan, who hypothesized that polypropylene tape may be rejected after transvaginal implantation via the TVT procedure and proposed a study to investigate the frequency, severity, histological, and immunochemical evidence of rejection.[135,136] Dr. Wang requested funding from Ethicon for this study and although there was some lack of support for Dr. Wang's study proposal at Ethicon,[137] funding ultimately was approved in December 2002.[138] Study results were published two years later, as follows.

Fifteen (15) of 670 TVT patients had sling erosion, defined as defective vaginal healing, for a 2.2% rate of defective vaginal healing post TVT procedure. Conservative treatment, including sitz bath with warm saline solution and local application of neomycin sulfate ointment, was first prescribed for these patients. Those who did not respond to conservative management underwent one or two debridements, i.e., "excision of the inflammatory/granulation tissue and simple closure of the vaginal wound with the suburethral part of the tape embedded."[139] For seven patients, the vaginal wall had not healed four weeks after the second debridement, and the exposed mesh was excised. These wounds healed after mesh explantation, resulting in a persistent defective healing (PDH) incidence of 1%[140] one to seven years after the operation. The authors comment that vaginal erosion may occur after delayed infection of the mesh or prominent foreign body reaction, leading to separation of the vaginal incision and mesh erosion. For the seven women who underwent two debridements and mesh excision, histopathologic findings suggested an immunologic reaction to the polypropylene mesh. Mesh constituents were fragmented and exhibited predominant foreign body reaction, dense fibrosis, and occasional perivascular mononuclear cell infiltration. "The results of this pilot study suggest that polypropylene mesh is not always biologically inert." The authors further noted that "[b]ecause a large and still increasing number of continence taping procedures have been undertaken, there is a clinical and theoretic basis for concern."[141]
Yet Gregory Jones, former Director Regulatory Affairs at Ethicon,[142] testified that if he received this information concerning a pattern of adverse events potentially representing rejection of the TVT mesh in 2002, it would have been of concern to him. However, the IFU for the TVT was

[135] ETH.MESH.00409657: Study Synopsis by Alex C. Wang, MD: Rejection of Polypropylene Tape After the Tension-Free Vaginal Tape (TVT) Procedure.
[136] ETH.MESH.00409670: Email series November 14-December 3, 2002, initiated by Martin Weisberg, RE: Prolene rejection.
[137] ETH.MESH.08793207 at 207-208: Email series October 29-November 11, 2002, initiated by Mark Sumeray, Vice President Clinical Trials, Ethicon Franchise, to Martin Weisberg, RE: Dr. Wang's proposal.
[138] ETH.MESH.00409659 at 660: Customer Initiated Grant Request by Alex C. Wang, MD, approved December 19, 2002.
[139] ETH.MESH.00523348 at 349: Wang AC et al. A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: A prospective case-controlled pilot study. American Journal of Obstetrics and Gynecology 2004;191:1868-74.
[140] ETH.MESH.00523348 at 350: *Id*.
[141] ETH.MESH.00523348 at 353: *Id*.
[142] ETH.MESH.08164608: Gregory Jones resume.

never updated to include this information.[143] Dr. David Robinson testified there is nowhere in the package insert that tells doctors there is a chronic foreign body reaction as a result of the TVT mesh, but, instead, the insert says the foreign body response is transitory.[144]

B. Mesh Shrinkage/Contraction and Associated Morbidities

For all implanted synthetic mesh, there is the issue of inflammatory response and foreign body reaction, as discussed above, particularly as regards the scale, severity, and chronicity of the reaction. The foreign body reaction can lead to scar plate formation resulting in various morbidities, including mesh erosion, pain, and dyspareunia. A chronic rather than an acute inflammatory response/foreign body reaction may result in failure of the device to perform not only safely but effectively.

All of the TVT meshes for stress urinary incontinence are comprised of original, old-construction Prolene mesh 6-mil fiber, with a mass per unit of 100 to 110 grams per meter squared,[145] which is considered heavyweight mesh.[146] A number of companies have developed new mesh systems as a result of increasing numbers of reported mesh-related complications in an effort "to increase efficiency and patient comfort and decrease the side effects and amount of foreign material left in the patient."[147] Ethicon is among those companies and has developed lighter-weight, larger-pore mesh in order to decrease the amount of foreign material left in the body, notably, "[b]ecause the more foreign material that's left in the tissue, the greater the foreign body reaction," which "can create a greater inflammatory reaction" leading to patient complications.[148]

Dr. Holste, whose job at Ethicon is "to evaluate the preclinical safety of a material within the framework of the development,"[149] affirmed that "[o]ne of the problems that a greater inflammatory reaction can cause in the human tissue to a foreign body like a polypropylene mesh implant is that there can be more contraction, sometimes known as mesh shrinkage."[150] "The formation of scar tissue throughout the mesh causes a contraction within the tissue. Since the mesh is compressible along its length it can be acted on by the tissue." This is the cause for shrinkage, not that the mesh itself shrinks.[151] "…[S]hrinkage rate is influenced by many parameters as the degree of fibrotic reaction is dependent on the mesh material/weave/width etc."[152] It appears, based on internal documents, that the "rule of thumb" regarding the amount of shrinkage occurring with the TVT mesh was 30%. [153]

Dr. Holste acknowledged, based on almost 30 years of working at Ethicon on tissue reaction to meshes, that greater inflammatory reaction can entrap nerves, leading to pain, and can cause

[143] Gregory Jones deposition, August 20, 2013, 117:13-118:13.
[144] Dr. David Robinson deposition (rough transcript), September 11, 2013, 280:5-11.
[145] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 38:21-39:6.
[146] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 40:12-15.
[147] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 51:3-12.
[148] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 51:25-52:22.
[149] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 144:20-23.
[150] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 52:23-53:6.
[151] ETH.MESH.03910418 at 420: Email series November 22-26, 2002, RE: Mini TVT – mesh adjustment.
[152] ETH.MESH.03910418: *Id*.
[153] *Id.*

erosions.[154] A heavier-weight mesh like the TVT Prolene mesh results in a greater foreign body reaction and, thus, "will cause a greater inflammatory reaction than a lighter-weight mesh,"[155] which can cause an increased risk of tissue contraction as compared to lighter-weight meshes,[156] during maturation of the collagenous tissue.[157]

The border for scar plate formation in small-pore, standard-weight meshes like the TVT mesh is around 1,000 microns (i.e., one millimeter). Because the pores of TVT mesh are less than one millimeter, the TVT mesh is susceptible to fibrotic bridging and scar plate formation.[158] Dr. Holste agreed that a lightweight, large-pore mesh would have less of an inflammatory response in the tissues around the urethra and there should be concern that heavyweight, small-pore meshes could result in "shrinkage and contraction problems in the tissues underlying the urethra for slings."[159,160] "Yet Ethicon never studied the difference between a lightweight, large-pore mesh in the tissue in and around the urethra for slings versus its old-construction, very first Prolene surgical mesh."[161]

C. TVT Mesh Fraying, Particle Loss, Roping and Deformation and Associated Morbidities

As discussed above in Section V.B., in October 2001 a modification to the TVT System was 510(k)-cleared that provided for the use of blue-pigmented Prolene polypropylene mesh. "[T]he mesh color was changed from clear to blue to assist in seeing the final mesh placement better."[162] "The reason for going to blue was so that the surgeon could see it under the urethra."[163] However, Ethicon documentation reveals that "[f]raying is inherent in the product based on the mesh construction. When any amount of tension is applied to the mesh, fraying occurs. Stretching of the mesh increases the probability of fraying and so apparition of mesh particles."[164] Dan Smith, currently an engineering fellow (June 2013) and an Ethicon employee for 36 years,[165] acknowledged that the mesh fraying "was known to us. It was known to our competitors."[166] "This is not new, and was exactly the original issue that stopped TVT blue for months."[167] The blue color made the particle loss apparent.

A marketing communication from the Director Marketing Europe, Steve Bell, advised that "[a]s more and more customers now move to TVT Blue…you may sometimes hear. 'I can see small blue

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[154] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 55:22-56:13.
[155] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 56:15-21.
[156] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 56:23-57:4.
[157] Joerg Holste, DVM, PhD, deposition, July 30, 2013, 588:23-589:11.
[158] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 62:21-63:1; 78:9-15; 80:7-81:4.
[159] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 116:10-18.
[160] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 156:7-20.
[161] Joerg Holste, DVM, PhD, deposition, July 29, 2013, 156:22-157:4.
[162] ETH.MESH.00858252: MEMO from Allison London Brown to Dan Smith RE: Mechanical Cut vs. Laser Cut Mesh Rationale (undated).
[163] Daniel Smith deposition, June 5, 2013, 177:18-21.
[164] ETH.MESH.03535750: Letter to Mr. Herve Fournier, Ethicon France, from Carol Holloway, Product Complaint Analyst, Worldwide Customer Quality, RE: 810041B TVT Device, Blue Mesh, Reference #6167, our file #30005383, October 12, 2005.
[165] Daniel Smith deposition, June 5, 2013, 28:18-23.
[166] Daniel Smith deposition, June 5, 2013, 160:3-10.
[167] ETH.MESH.00863391: Email series February 27, 2004, From Bernhard Fischer to Janice Burns to Dan Smith, latter's reply, RE: Important: 2 TVT Complaints concerning allegedly brittle mesh.

pieces come off the mesh! What's wrong.'"[168] In regards to this marketing communication, Dan Smith noted in correspondence with Medical Director Charlotte Owens concerning logging complaints that some customers had raised questions "about the blue particles again (the same as when it was released in the states)."[169] This marketing communication made several key points, among which was the following: "The **same** number of particles came off the clear mesh when it was stretched – It's just that you see them against the tissues and skin more when they are blue. – *This is no different to what has happened for the past 7 years with TVT."*[170] Significantly, I found no evidence that mesh fraying with particle loss was noted in the TVT labeling or anywhere in either of the TVT 510(k)s: K974098 and K012628. To the contrary, both 510(k)s state that "[t]he material is not…subject to degradation…"[171]

Thus, it is particularly noteworthy that a few months prior to the submission of 510(k) Number K012628, in response to a complaint about "uneven/inconsistent tape width as well as fraying edges," from Dr. Alex Wang in Taiwan, "one of the most experienced TVT users in the world," Medical Director Dr. Martin Weisberg remarked, "…I don't think we have any idea whether the tape inconsistencies are clinically significant or not, however the appearance of the tape in the appended pictures certainly gives the impression of inconsistent manufacturing and/or quality control."[172] Richard Isenberg further commented, "I agree with Marty. Consistency in manufacturing appears to be at issue. I cannot judge clinical significance from the information available to me…"[173]

The referenced marketing communication further recommended to "[r]eassure your doctors that this is part of the success of TVT. The way we have cut the mesh makes the edges softer and we feel that this has been a crucial success factor in TVT. Reassure them that PROLENE is proven to be inert and there are hundreds of papers going back 25 years to reinforce this point. These particles will not cause any problem."[174] Notably, as discussed above, polypropylene is not biologically inert. When Dan Smith was asked, "So using inert in a technical sense, this is false, isn't it?," he replied, "I probably would have used a different word." Yet it appears "this is what Steve Bell was telling the salespeople to go out and tell doctors."[175]

I reviewed no evidence of any studies conducted to determine long-term whether the fraying and the particles lost inside the body might cause deleterious effects. Instead, as discussed in Section X.D.2., there were complaints related to mesh fraying and particle loss that should have been submitted to FDA as MDR reports in my professional opinion but were not; nor did I review any evidence of follow up of these complaints to determine if there were any long-term sequelae or impact of mesh fraying on TVT effectiveness. Concerns of physicians regarding the mesh fraying are highlighted by a communication from Dr. J. Eberhard, considered an opinion leader in

[168] ETH.MESH.00865322 at323: Email series March 2, 2004, between Dan Smith and Charlotte Owens, RE: Reminder on BLUE mesh!
[169] ETH.MESH.00865322: *Id.*
[170] ETH.MESH.00865322 at323: *Id.*
[171] ETH.MESH.08476210 at 224: 510(k) Number K974098; ETH.MESH.00748310 at 341: 510(k) Number K012628.
[172] ETH.MESH.03905472 at 473-474: Email series April 23-June 6, 2001, initiated by Richard Hu, Johnson & Johnson Medical Taiwan, RE: TVT recommendation from Dr. Alex Wang.
[173] ETH.MESH.03905472: *Id.*
[174] ETH.MESH.00865322 at 323: *Id.*
[175] Daniel Smith deposition, June 5, 2013, 181:4-11.

Switzerland.[176] Dr. Eberhard returned a TVT tape used for demonstration for patients before their surgery, remarking as follows:

> "Already at the operation it is embarrassing to see how the tape is crumbling. But it gets worse if there is a stretch on the tape.
>
> It is urgent that Johnson & Johnson quickly produce a tap [sic] that is solid and weaved. If not I have the convenience that the doctors will change the taps [sic] and will get others (from other suppliers).
>
> I can't understand, that no one will solve that problem for such a long time. At the latest, as the tap [sic] has becoming blue, everyone has realized that the quality of the tape is terrible…"[177]

In August of 2006, Gene Kammerer, an Ethicon Engineering Fellow, described in a powerpoint including photos how the TVT mechanically cut mesh responded when stretched 50%. He describes and the photos depict significant degradation, loss of structure, fraying, roping and deformation that occurs to the mechanically cut mesh as opposed to the laser cut mesh (LCM).[178] Roping of the TVT mesh was known to Ethicon and was a source of frequent complaints from physicians.[179] In fact, some at Ethicon felt that TVT was losing business daily because of the mesh elasticity and roping.[180]Peer reviewed literature supports that the TVT easily becomes permanently deformed with very little tension when compared to other polypropylene slings.[181]

Thus it was, effective fourth quarter 2006, that Ethicon moved from mechanical cut mesh (MCM) to also making LCM available.[182] It was announced that this change was made to gain efficiencies in manufacturing processes but the announcement also noted that it was found that laser cutting "reduced particulate loss as well as the potential for mesh fraying."[183] The announcement of the availability of LCM (dated as approved on June 26, 2006) advised that "[t]he laser cut mesh will be available for you to sell as needed, particularly to customers that have voiced concerns regarding particle loss and fraying."[184] Notably, the Clinical Expert Report signed by both Dr. Martin Weisberg and Dr. David Robinson[185] in regards to the laser cut mesh notes that "the need for

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[176] ETH.MESH.02180826-827: Email series November 12, 2004, between David Menneret, Complaint investigator/Regulatory contact, and Sibylle Basso, RE: Dr EBERHARD letter.
[177] ETH.MESH.02180833: Translation of PD Doctor Eberhard's letter of 18.10.04.
[178] ETH.MESH 03334244; ETH.MESH.06001408: LCM Project Photographs Comparing Laser Cut Mesh vs Mechanical Cut Mesh; ETH.MESH.00584527: Second half of photo presentation Re: Degradation
[179] ETH.MESH 00526473: Email from Allison London Brown states the Ethicon gets a high number of complaints of the material stretching "to the point of being a string."
[180] ETH.MESH.00440005: Emails Re: Important Laser cut mesh update.
[181] Moalli et al., Tensile properties of five commonly used mid-urethral slings relative to the TVT, *Int. Urogynecol*, 2007.
[182] ETH.MESH.00167119: Product Pointer – GYNECARE TVT Tension-free Support for Incontinence, Approved June 26, 2006, by Marketing Services.
[183] *Id.*
[184] *Id.*
[185] ETH.MESH.00167104: Clinical Expert Report – Laser Cut Mesh for GYNECARE TVT Tension-free Support for Incontinence, GYNECARE TVT Tension-free Support for Incontinence with Abdominal Guides, and GYNECARE TVT Obturator System Tension-free Support for Incontinence, April 18, 2006.

switching from mechanically cut to laser cut mesh arose as a response to customer needs. Customers expressed a desire for a TVT mesh with smoother edges rather than edges with the ends of individual fibers exposed. Customer feedback also indicated that there was some dissatisfaction with the potential fraying effect of mechanically cut mesh."[186] The announcement of availability of the laser cut mesh noted that "the edges of the mesh will appear and may feel slightly different upon stretching," stating that several bench tests were conducted and "the physical properties of both the mechanically cut and laser cut meshes are similar within the range of physiologic forces."[187]

Design verification "shows that sample sets were not statistically different, however the avg% particle loss of MCM is higher than LCM."[188] Testing showed that "[o]n average, the Mechanically Cut mesh lost approximately twice the number of particles as the Laser Cut mesh."[189] Notably, using "the test method from the new French standards for particle loss, the difference between TVT and the competitors is significant. Approximately 10 fold more for TVT at 8% of the strip falling off."[190]

"Qualitative one-on-ones on the topic of Laser Cut Mesh vs. traditionally cut mesh were completed the weekend of Dec 10-11 (year not specified) with several preceptors: Dr. Vince Lucente, Dr. David Robinson, Dr. Dennis Miller, Dr. Jim Raders, Dr. Bob Rogers, Dr. Jaime Sepulveda, Dr. Chip Hanes and Dr. Aaron Kirkemo."[191] With regard to "denaturing/linting," four of these doctors had experienced "previous personal issues with the linting factor. But all expressed concern with it on behalf of other colleagues who may have experienced negative problems with it. Dr. Rogers made note that some peers may replace the first mesh if the linting occurs, as they are concerned with leaving particles in their patient. Dr. Sepulveda said that he had noticed the linting in patients after their next-day adjustment."[192]

The evidence is clear that Ethicon knew early on that the TVT mesh had many characteristics that could lead to adverse outcomes for patients, including that the mesh had frayed edges, lost particles, could deconstruct, deform and rope. In fact, Ethicon's Design Failure Mode Effects Analysis (dFMEA) completed in preparation for launch of the LCM, identified "roping" or "deconstruction" of the mesh as causes of erosion and, further, identified the roughness of the edges of mesh as a cause of pain.[193] Reduction in pore size is also listed as a potential cause of

[186] ETH.MESH.00167104 at 107: *Id.*
[187] ETH.MESH.00167119: Product Pointer – GYNECARE TVT Tension-free Support for Incontinence, Approved June 26, 2006, by Marketing Services.
[188] ETH.MESH.00585842: Email series RE: TVT LCM – particle loss (reimbursement submission), from Sungyoon Rha, response from Gene Kammerer.
[189] ETH.MESH.00167104 at 108: Clinical Expert Report – Laser Cut Mesh for GYNECARE TVT Tension-free Support for Incontinence, GYNECARE TVT Tension-free Support for Incontinence with Abdominal Guides, and GYNECARE TVT Obturator System Tension-free Support for Incontinence, April 18, 2006; BE-2005-1920 Protocol to Evaluate Elongation, Particle Loss and Flexural Rigidity of TVT U PROLENE Mesh Laser-Cut vs. Mechanical-Cut.
[190] ETH.MESH.00585842: Email series RE: TVT LCM – particle loss (reimbursement submission), from Sungyoon Rha, response from Gene Kammerer.
[191] ETH.MESH.01809082: Memo: VOC on new Laser Cut TVT Mesh (undated).
[192] ETH.MESH.01809082 at 83: *Id.*
[193] ETH.MESH 01218019; Dan Lamont testified that the fraying of the mesh is a defect (Dan Lamont deposition,, Sept.11, 2013.

erosion and it was known by the company that reduced pore size can lead to erosions.[194] Despite Ethicon's knowledge of these problems with the mesh, Ethicon decided to continue marketing the TVT mechanically cut mesh even after the LCM mesh was launched and never informed physicians or patients about these risks from the mesh characteristics in its labeling.

D. Biocompatibility Testing and Cytotoxicity

For the TVT System initial 510(k) (K974098), Ethicon determined that "[t]he long clinical experience with PROLENE mesh indicated the cytotoxicity testing would be sufficient to support biocompatibility of this component."[195] Cytotoxicity testing was conducted in accordance with ISO 10993-5 guidelines: "Biological Evaluation of Medical Devices – Tests for Cytotoxicity: In Vitro Methods."[196] The polypropylene mesh component of the sterile TVT device was noncytotoxic in the ISO Agarose Diffusion test but showed moderate to severe cytotoxicity in the ISO Elution test, suggesting cytotoxic potential in this sensitive test system. Of note, previous ISO Agarose Diffusion and ISO Elution cytotoxicity testing of normal production sterile PROLENE mesh indicated this material was noncytotoxic. Nonsterile raw material polypropylene mesh used in the manufacture of the TVT device was also noncytotoxic in the ISO Elution test.[197] Based on my review of the TVT 510(k), Ethicon failed to report to FDA the corroborating results of marked cytotoxicity of the TVT mesh which were observed by Ethicon Scotland in both the ISO Elution test and the ISO Agar Overlay test of the sterile Ulmsten device.[198] Ethicon concluded that "the long history of safe clinical use of [polypropylene] as mesh and suture products suggests strongly that this material is inherently biocompatible, and that the potential cytotoxicity observed is self-limiting and minimal when compared to the implantation procedure itself."[199] It is noteworthy that Ethicon also evaluated the cytotoxicity of competitor products, specifically, the Bard mesh and Surgilene suture, and those products were found to be non-cytotoxic.[200]

Additionally, Ethicon reported to FDA that "[p]olypropylene mesh has been used extensively in humans for many years without clinical evidence of rejection and has proven to be one of the most inert materials implanted in humans." Further, "the healing that occurs over exposed mesh provides strong clinical evidence that this material does not impair wound healing and is not cytotoxic in humans. Implantation of a potentially cytotoxic material would be expected to cause impaired wound healing resulting in non-healing ulcerations and overt evidence of foreign body reaction. Thus, this clinical data provides significant evidence that the potential cytotoxicity of the polypropylene mesh observed in-vitro does not translate into any clinical significance or adverse patient outcomes."[201] Thus, it is important to note that impaired wound healing/wound dehiscence was reported in 3.8% of the TVT MDR reports reviewed on the MAUDE database from 1999

[194] Joerg Holste deposition July 29, 2012, 51:25-56:13; David Robinson deposition September 11, 2013, 1066:8-1070:22.
[195] 510(k) Number K974098: Biocompatibility Testing Results, page 40.
[196] *Id.*, page 41.
[197] 510(k) Number K974098: Biocompatibility Testing Results, page 41.
[198] ETH.MESH.06852118 at 121: Review of Biocompatibility Data on the Tension Free Vaginal Tape (TVT) System for Compliance to FDA G-95/ISO 10993/EN 30993, May 26, 2000, from Richard W. Hutchinson, DVM, PhD, Senior Scientist, Preclinical Safety Assessment, to P. Cecchini.
[199] *Id.*
[200] Dr. David Robinson deposition (rough transcript), September 11, 2013, 288:22-289:8.
[201] *Id.*, page 42.

through 2010. Moreover, mesh erosion and exposure are frequently reported complications of polypropylene mesh, including the TVT device, and were reported in 32.1% of TVT MDR reports reviewed on the MAUDE database from 1999 through 2010. Additionally, as discussed above, Wang et al.,[202] reported a 2.2% rate of defective vaginal healing post TVT procedure in a series of 670 patients implanted with the TVT device and a persistent defective healing rate of 1%. This clinical evidence contradicts Ethicon's statement to FDA that the observed cytotoxicity does not have clinical significance or adverse patient outcomes.

It is remarkable that Dr. David Robinson testified that he never knew during the time he was "the Worldwide Medical Director at Ethicon that there was positive cytotoxicity of the polypropylene mesh used in the TVT product."[203] Notwithstanding the positive cytotoxicity results and the clinical evidence of precisely the types of adverse events Ethicon advised FDA it would expect from cytotoxic material, Dr. Robinson testified he was not aware of any long-term study undertaken by Ethicon to determine whether or not the TVT mesh is clinically cytotoxic in women.[204]

E. Potential for Carcinogenicity as a Result of Chronic Inflammation

Chronic inflammation may predispose to cancer and there are a number of examples of inflammatory conditions associated with cancer in humans, including *H. pylori* and gastric cancer, asbestos and mesothelioma, and hepatitis virus B or C and hepatocellular carcinoma.[205] This may occur via the action of proinflammatory cytokines on cells that have already sustained genetic damage (initiation) but are not yet malignant. Inflammatory cytokines are known to have tumor promoting activity. It is not known whether inflammatory cytokines can cause an initiating event.

Infection is a documented complication of mesh implants, including SUI slings.[206] Implantation may also potentiate an existing infection. Since the body mounts an inflammatory response to infection, chronic or sub-chronic infections may result in long-term inflammation. There is a lack of long-term data in the literature about chronic infection/inflammation after mesh implantation. Most infections are acute, early postoperative complications. However, Dr. Holste testified that it is known that biofilms can attach to meshes, resulting in development of chronic infections and, thus, chronic inflammation which can cause future complications.[207] [Note that a biofilm is "an assembly of bacterial colonies fixed upon a support and locked up into an encapsulating matrix" and resistant to stress and antimicrobials. "Progressively, with (sic) any clear signs of inflammation or infection, the prosthesis will loosen. The microorganisms involved in most cases are common, Staph. A and Staph. E."[208]]

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[202] ETH.MESH.00523348 at 349-350: Wang AC et al. A histologic and immunohistochemical analysis of defective vaginal healing after continence taping procedures: A prospective case-controlled pilot study. American Journal of Obstetrics and Gynecology 2004;191:1868-74.
[203] Dr, David Robinson deposition (rough transcript), September 11, 2013, 286:3-9.
[204] Dr. David Robinson deposition (rough transcript), September 11, 2013, 293:5-11.
[205] Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 2005;7:211-217.
[206] FDA Executive Summary. Surgical mesh for treatment of women with pelvic organ prolapse and stress urinary incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting September 8-9, 2011.
[207] Joerg Holste, DVM, PhD, deposition, July 30, 2013, 298:7-14.
[208] Joerg Holste, DVM, PhD, deposition, July 30, 2013, 296:24-297:22.

There are two case studies in the literature in which tumors developed in patients with mesh implants. These are discussed below.

The first case study describes a female patient who presented with gross hematuria, urinary urgency and frequency and dysuria 10 weeks after placement of TVT (Gynecare) for urodynamically confirmed SUI.[209] Comparison CTs confirmed that the mass was not present during TVT placement. She was eventually diagnosed with an inflammatory myofibroblastic tumor (IMT) and underwent a transurethral resection with complete resolution of symptoms and no recurrence two years later. IMTs are typically characterized by a mix of inflammatory cells, e.g., plasma cells, lymphocytes and eosinophils, and bland spindle cells without nuclear atypia. The patient's tumor was composed of fascicles of spindle cells with areas of variable cellularity and prominent myxoid change, consistent with IMT. Although rare, postoperative IMTs have been known to follow manipulation of the bladder by biopsy, injury or resection. Postoperative IMTs have also been shown to follow prostate biopsy or resection. This is the first report of such an occurrence after TVT placement. Whereas the patient did not have a visible bladder injury at the time of mesh placement, it is possible that the muscularis layer may have been inadvertently breached without actual perforation. This patient also had a history of neurofibromatosis, but the authors state that no information in the literature suggested a relationship between that condition and the IMT.

The second study describes two male patients who developed squamous cell carcinoma (SCC) years after having mesh hernia repairs.[210] In each case, the SCC was associated with an underlying long-term infection due to the mesh. The first patient had a 24-year history of mesh infection (type of mesh and date of implant not reported). In 1988, he underwent multiple laparotomies due to biliary pancreatitis, leaving exposed mesh. From 2003 to 2007 he underwent several interventions to remove exposed pieces of the mesh, after the last of which he developed an intermittent enteric fistula. In 2012 he was diagnosed with SCC and fluid from his abdominal wall was positive for methicillin-resistant *Staphylococcus aureus*. Resection of the tumor included two segments of the small bowel, part of the transverse colon and removal of the infected mesh. He received adjuvant chemotherapy and his preliminary outcome six months after surgery was good. The second patient had a 6-year history of mesh infection. Following laparotomy for a closed abdominal trauma, he developed an incisional hernia that was treated with polyester mesh reinforcement. One year later the mesh became infected and was partially exposed. Five years after this, he presented with an ulcerated lesion of the skin around the exposed mesh, which was diagnosed as SCC. He underwent resection of the tumor and reconstruction of the abdominal wall, but had a recurrence six months later. Further interventions were unsuccessful and the patient died due to progressive SCC after four months. In both cases, it was felt that the SCC arose in response to long-term infection of exposed mesh, not directly because of the mesh itself.

Although mesh has not yet been implicated as a carcinogen in humans, the known complication of chronic infection as a result of mesh implantation may give rise to other cases of malignancy as a secondary outcome. Polypropylene implants can give rise to local sarcomas in rats,[211] and while

[209] Kwon SY, Latchamsetty KC, Benson J, Carreno M. Inflammatory myofibroblastic tumor of the urinary tract following a TVT. Female Pelvic Med Reconstruct Surg 2012;18:249-251.
[210] Birolini C, Minossi JG, Lima CF, Utiyama EM, Rassian S. Mesh cancer: long-term mesh wall infection leading to squamous-cell carcinoma of the abdominal wall. Hernia, published online 19 April 2013.
[211] Sunoco Material Safety Data Sheet for C4001 Polypropylene. November 20, 2006.

this may not be predictive of human outcomes, there is sufficient evidence of a potential signal to support that manufacturers should perform preclinical carcinogenicity testing of implanted polymers prior to marketing a device. Regardless, the fact that the polypropylene contained in the TVT caused sarcomas in rats should have been disclosed to physicians and patients.

OPINION #1: Failure to Conduct Appropriate Testing

The above information and discussions concerning the potential for persistent foreign body reaction and chronic inflammation, mesh degradation, cytotoxicity, chronic infection leading to chronic inflammation, loss of pore size of the mesh, and the potential for carcinogenicity highlight numerous potential concerns of TVT mesh implantation about which Ethicon not only failed to warn healthcare practitioners and patients but also failed to investigate through appropriate testing. The initiation of the World Registry study was a positive step but, as discussed above, this study was discontinued with no long-term data to address these outstanding concerns potentially impacting not only patient safety but also product effectiveness.

Regarding cytotoxicity, it is notable that Ethicon selected the best data for disclosure to FDA and, thus, did not submit study data that showed marked cytotoxicity in both types of cytotoxicity studies conducted (ISO Elution test and ISO Agar Overlay test conducted by Ethicon Scotland). I reviewed no evidence that Ethicon performed additional testing to elucidate the reasons for the cytotoxicity of the sterile TVT mesh as compared to the non-cytotoxicity of normal production sterile PROLENE mesh and nonsterile raw material polyprolylene mesh. [212]

With regard to mesh fraying and particle loss, I have not seen any evidence of any studies conducted to determine long-term whether the fraying and the particles lost inside the body might cause deleterious effects.

In these multiple ways in my professional opinion, Ethicon failed to perform testing that was critical to learning the long-term safety of the TVT permanent implant. Ethicon fell below the standard of care required of a reasonably prudent medical device manufacturer. Moreover, Ethicon failed to comply with its own credo, specifically, that the company's first responsibility is to the doctors and patients who use Ethicon's products."[213]

VII. TVT CLASSIC: KNOWN/KNOWABLE RISKS

A. Known Potential Complications: Synthetic Mesh in SUI Repair

1. Source: Ethicon Internal Documents and Deposition Testimony

Testimony of Ethicon senior management in both Medical Affairs and Regulatory Affairs confirms that all the risks of the TVT System known today were also known at the time of TVT launch.[214,215]

[212] Thomas Barbolt deposition August 14, 2013 86:4-14; 319:19-21
[213] Exhibit T-115 (no Bates number): Johnson & Johnson credo.
[214] Catherine Beath, July 12, 2013, 608:13-20.

For example, Dr. Piet Hinoul, currently Medical Director worldwide for the Ethicon energy franchise,[216] testified that Ethicon knew all of the potential complications listed below at the time of the TVT launch. This list includes all of the complications associated with transvaginal placement of surgical mesh that were identified in FDA's 2008 *Public Health Notification*. (Please reference Section IX.A.) Both Catherine Beath, Vice President of Quality Assurance and Regulatory Affairs, and Dr. Hinoul testified that Ethicon knew about all of the following complications identified in the 2008 *PHN* at the time of product launch.[217,218]

Dr. Hinoul agreed that all of these complications should be reflected in the TVT labeling; indeed he said "they will be reflected"[219] or "are included in the labeling."[220] Dr. Arnaud agreed it was very important for the company to communicate the known risks of the company to physicians so they would know what they are and to make sure the risks are communicated to patients.[221]

As discussed in Section VIII.A., a number of these complications are not in the TVT labeling, contrary to Dr. Hinoul's testimony.

E. Mesh erosion, e.g., through the vaginal epithelium (with potential for significant pain)
F. Infection
G. Pain
H. Urinary problems
I. Recurrence of incontinence
J. Bowel perforation
K. Bladder perforation
L. Blood vessel perforation
M. Vaginal scarring
N. Dyspareunia[222]

Dr. Hinoul "absolutely" agreed that Ethicon knew at the time of TVT launch that some patients could have complications or failures that would require additional surgery(ies)[223] or other treatments, including intravenous (IV) therapy, blood transfusions, or drainage of hematomas or abscesses.[224] Further, he and Dr. Arnaud acknowledged that Ethicon anticipated the possibility from the time of the TVT launch that a patient might have a TVT implanted and subsequently experience pain, erosion, or other complications that would necessitate removal of the TVT mesh.[225]

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[215] Dr. Piet Hinoul deposition, June 27, 2013, 551:12-552:9.; Dr. Axel Arnaud deposition, July 19, 2013, 125:15-127:1.
[216] Dr. Piet Hinoul deposition, June 26, 2013, 12:24-13:5.
[217] Catherine Beath, July 11, 2013, 233:25-234:8; 245:21-246:1.
[218] Dr. Piet Hinoul deposition, June 27, 2013, 551:12-552:9.
[219] *Id.*, 556:25-557:7.
[220] *Id.*, 557:23-558:4.
[221] Dr. Axel Arnaud deposition, July 19, 2013, 19:25 -21:1.
[222] Dr. Piet Hinoul deposition, June 27, 2013, 547:5-552:9 (testimony inclusive of all complications listed through dyspareunia).
[223] *Id.*, 552:14-21.
[224] *Id.*, 556:3-12.
[225] *Id.*, 554:14-555:11; See also Deposition of Dr. Axel Arnaud for list of known complications including pain, dyspareunia, wound healing difficulties, voiding difficulties, contraction. Deposition of Dr. Axel Arnaud, July 19, 2013, 115:9-127:1.

Ethicon internal documents[226,227] and related testimony[228] provide evidence that Ethicon knew not only about the above-listed potential complications of TVT implantation but also the additional complications listed below "at the time of the launch of the TVT Classic"[229] and, thus, prior to implementation of the first in-use version of the IFU available for review (i.e., in use September 8, 2000).

- Inflammation at the surgical site[230]
- Urinary tract infection (UTI)[231]
- Abnormal postoperative bleeding,[232] including hematoma[233]
- Dysuria[234]
- Hematuria[235]
- De novo detrusor instability or urgency[236]
- Irritation at the wound site[237]
- Fistula formation[238]
- Urethral obstruction due to over-correction with resultant urinary retention[239]
- Venous thrombosis[240]
- Abscess formation[241]

Dr. Hinoul acknowledged that mesh exposure and mesh erosion can be caused by a foreign body response, although he does not consider the foreign body response itself a complication.[242] It is important to note that the risk of erosion of the TVT mesh is a lifelong risk.[243] As Dr. Hinoul pointed out, the device is a foreign body and doesn't resorb, so the mesh can erode into the vaginal wall (termed "exposure") or into the urethra[244] or bladder.[245] Erosions can also be recurrent.[246]

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[226] ETH.MESH.03905059 at 069: Draft Clinical Expert Report GYNECARE TVT SECUR System, August 23, 2005, Section 8: Potential Complications.
[227] ETH.MESH.00658177 at 189-191: Surgeon's Resource Monograph – Expert opinions on the use of GYNECARE TVT Tension-Free Support for Incontinence, A REPORT of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases.
[228] Dr. Piet Hinoul deposition, June 27, 2013, 559:20-560:19.
[229] *Id.*, 575:3-16.
[230] *Id.*, 562:1-3.
[231] *Id.*, 562:16-19.
[232] *Id.*, 562:20-22.
[233] *Id.*, 566:25-567:23.
[234] *Id.*, 562:23-24.
[235] *Id.*, 563:7-9.
[236] *Id.*, 564:10-13.
[237] *Id.*, 565:9-12.
[238] Dr. Piet Hinoul deposition, June 27, 2013, 566:11-14.
[239] *Id.*, 566:15-19.
[240] *Id.*, 567:24-568:4.
[241] *Id.*, 568:13-15.
[242] *Id.*, 566:1-9.
[243] In addition, Ethicon's own long term study comparing TVT to Burch colposuspension concluded that "tape erosion may occur many years after surgery." Ward et al., Tension-free vaginal tape versus colposuspension for primary stress incontinence 5-year follow up, *BJOG*, 2007.
[244] Dr. Piet Hinoul deposition, June 27, 2013, 582:3-9.
[245] *Id.*, 576:18-577:1.
[246] *Id.*, 577:7-15.

Ethicon's former Medical Director also agreed that narrowing of the vaginal wall, while the anticipated risk was very low, could occur and was a known risk at the time of the TVT launch.[247] As noted by Dr. Hinoul, mesh contracture resulting from contraction of the scar around the mesh was a risk Ethicon considered at the time of the TVT launch.[248] He conceded that in rare instances such contracture "can cause pain and significant discomfort for the patient."[249] Moreover, he acknowledged that pain can be chronic and difficult to treat.[250] Ethicon also knew of the possibility that nerve damage could cause lifelong pain.[251] If such complications as chronic pain, dyspareunia, or other complications necessitate mesh removal, the removal "can prove to be a challenge" because of tissue ingrowth, and there can be "damage to tissue during the removal process or other complications related to the removal surgery."[252] While "[i]t would have seemed very unlikely," Dr. Hinoul affirmed that Ethicon considered the risk at the time of TVT launch that "some patients would suffer complications making it impossible for them to have comfortable sexual relations for the rest of their lives."[253] Dr. Weisberg also agreed that painful sexual intercourse was a risk of the TVT device that Ethicon was aware of at the time the product was launched in the United Staes in 1998,[254] Dr. Arnaud also agreed that the fact the mesh could erode into the vagina and cause dyspareunia or painful sexual intercourse was a risk he knew about at the time of launch.[255]

As regards inflammatory reactions to the mesh foreign body, Dr. Hinoul explained why "some patients will have more major inflammatory reactions from the foreign body, the mesh, than other patients."[256] Specifically, people respond to a foreign substance differently, as with allergies. So the way people form a scar will differ and, accordingly, scarring from a TVT mesh "may differ from one patient to another."[257]

Ethicon also knew at the time of TVT launch that a patient potentially could develop worse stress urinary incontinence or have a recurrence of incontinence following TVT surgery. As Dr. Hinoul testified, "It's inherent to incontinence surgery,"[258] as is voiding dysfunction. Dr. Hinoul and Dr. Arnaud affirmed that voiding dysfunction also was a known potential complication at the time of TVT launch.[259]

Approximately two years after TVT launch, in June 2000, a GYNECARE TVT Summit Meeting was held to "create a clear, consistent, and structured approach to training."[260] The Summit Meeting was directed by Dr. Vincent Lucente, Dr. Eric Kuhn, and Dr. Carl Klutke with the intent

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[247] *Id.*, 575:21-576:14.
[248] Dr. Axel Arnaud deposition, July 19, 2013, 122:3-12.
[249] Dr. Piet Hinoul deposition, June 27, 2013, 577:16-578:10.
[250] *Id.*, 577:12-14.
[251] *Id.*, 580:25-581:3.
[252] *Id.*, 578:12-579:4.
[253] *Id.*, 580:12-24.
[254] Dr. Marty Weisberg deposition, August 9, 2013, 714:1-716:3
[255] Dr. Axel Arnaud deposition, July 9, 2013, 116:21-119:9; 125:15-126:6
[256] Dr. Piet Hinoul deposition, June 27, 2013, 579:5-11.
[257] *Id.*, 579:13-21.
[258] *Id.*, 581:4-582:2.
[259] *Id.*, 582:10-583:1; Dr. Axel Arnaud deposition, July 19, 2013, 117:12-15.
[260] ETH.MESH.00658177 at 180: Surgeon's Resource Monograph – Expert opinions on the use of GYNECARE TVT Tension-Free Support for Incontinence, A REPORT of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases.

of creating a resource monograph for proctoring surgeons that defined the proper approach to GYNECARE TVT device training. The resource monograph that was developed as a result of this summit included the experience of more than 20 active proctors of the TVT system.[261] Included in the monograph is a discussion of potential complications, their causes and recommendations. The following specific complications are listed in this monograph: vaginal bleeding; retropubic hematoma; vaginal perforation during surgery; bladder perforations; inability to void after the procedure; injured urethra; urethral erosion; mesh protrusion (or defective healing); vascular injuries; bowel perforations; de novo urge and possibility of post-operative obstruction; infection of the mesh; urinary tract infection; and device failure. All of these complications are represented in the above listings and discussion of potential complications known to Ethicon at the time of TVT launch, except for one: vaginal perforation.[262]

After the FDA Public Health Notice (PHN) in 2008, Ethicon supplemented its statement of risks to patients, but never updated the risk information contained in the IFU.[263] Ethicon admitted that it knew about all complications referenced in the FDA's 2008 PHN and publically stated that all complications were already contained in its labeling.[264] Ethicon's actions thereafter support that Ethicon knew that information about serious and life changing complications associated with the TVT should be added to the labeling. Specifically, Ethicon supplemented its patient brochures (but not the IFU) to include additional risk information in late 2008, but the changes did not adequately warn of all known serious risks.[265] In early 2009, an Ethicon document reveals that employees discussed updating the IFU to include additional risk information and specifically noted "patient specific concerns", including that patients were not getting adequate risk/benefit information, concerns about erosions, about re-operations related to erosions, about dyspareunia and pain affecting patients' quality of life, and that the type and intensity of the post-operative complications were disproportionate to patients' pre-operative expectations.[266] Despite these internal discussions about updating the IFU, the IFU was not changed.

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[261] ETH.MESH.00658177 at 180: Surgeon's Resource Monograph – Expert opinions on the use of GYNECARE TVT Tension-Free Support for Incontinence, A REPORT of the June 2000 Summit Meeting, 17-surgeon panel representing more than 1200 cases.

[262] ETH.MESH.00658177 at 189-191: *Id*.

[263] ETH.MESH.08003279: Patient Brochure-Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living (2008); ETH.MESH.08003295: Patient Brochure-Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living (2011); ETH.MESH.09744858: Patient Brochure-Stop Coping. Start Living. What You Should Know About Stress Urinary Incontinence; ETH.MESH.05225354: Instructions for Use (IFU): TVT Tension-free Vaginal Tape; ETH.MESH.02340306: Instructions for Use (IFU): Gynecare TVT Tension-free Vaginal Tape; ETH.MESH.02340471 and ETH.MESH.05222673: Instructions for Use (IFU): Gynecare TVT Tension-free Vaginal Tape; ETH.MESH.02340504: Gynecare TVT Instructions for Use (IFU); ETH.MESH.03427878: Instructions for Use (IFU): Gynecare TVT Tension-free Support for Incontinence.

[264] ETH.MESH.07937824: Emails Re: Information about FDA notification on use of mesh in pelvic surgery; ETH.MESH.02310653: Email Re: Information about FDA notification on use of mesh in pelvic surgery, with FDA Public Health Notification to Healthcare Professionals attached; ETH.MESH.01706065: The Science of "What's Left Behind"…Evidence & Follow-Up of Mesh Use for SUI, PowerPoint Presentation; ETH.MESH.00669604: Data sheets showing PFR Rankings, CH Rankings, and UH Rankings. Review of the labeling at the time of Ethicon's statements about the PHN reveal that many of the complications in the PHN were not included in Ethicon's physician or patient labeling.

[265] Section VIII.B infra; (ETH.MESH.04093117: Emails Re: TVT IFUs on tape extrusion, exposure and erosion; ETH.MESH.08003279: Patient Brochure: Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living.)

[266] ETH.MESH.04081189: AE and complication of the Slings, Meeting Agenda.

When the FDA subsequently issued an update PHN in July of 2011[267], Ethicon once again supplemented risk information in its TVT patient brochure with necessary risk information, but again chose not to make any changes to the IFU.[268] As described in Section VIII.B, these changes to the patient brochure in 2011 and again in 2012 included information about the serious, life altering complications associated with the TVT – all of which Ethicon admits it knew even at the time of launch of the TVT product.[269] This information, and more, was necessary years earlier so that physicians and patients could have all the necessary risk information needed in order to perform a fully informed risk/benefit analysis.

2. Source: FDA MAUDE Database

As discussed in detail in Section X., an independent search/review of the Manufacturer and User Facility Device Experience (MAUDE) database was undertaken for the purposes of this Report, specifically, to evaluate the relevant serious adverse event information known or knowable to Ethicon from the MAUDE database (which includes MDRs submitted by Ethicon). The first date on which an MDR was recorded in the MAUDE database for the TVT device was 1999. Tabulations of the adverse events reported between 1999 through 2010 are presented for the reader's review in Exhibit 1. An assessment of these adverse events shows that the most frequently reported complications are representative of those discussed above.

3. Source: Scientific and Medical Literature

Prior to the initial marketing of TVT in 1998,[270] the literature relevant to the use of synthetic mesh for SUI repair was limited but provides evidence that the potential for specific complications associated with use of mesh was known or knowable to Ethicon. Three reviews on the surgical management of female stress urinary incontinence and/or the use of synthetic mesh in gynecologic surgery are presented below, along with a discussion of the complications reported in the clinical evaluations provided in the TVT 510(k) Number K974098: Ulmsten et al.; Eriksson (MEDSCAND) Scandinavian multi-center trial; Drs. Wang and Lo (Taipei, Taiwan); and Dr. Blaivas and Lauri Romanzi. Individual summaries of a number of relevant publications that span the time period from 1996 (Ulmsten et al. article) through 2012 are provided in Appendix C.

3.1 Literature Reviews

In 1997, the same year in which Ethicon submitted the TVT 510(k) premarket notification to FDA, Iglesia and colleagues[271] reviewed the use of synthetic mesh materials (including polypropylene) in gynecologic surgery. There were no randomized prospective trials available; all articles reviewed consisted of sacrocolpopexy, suburethral sling, or pelvic sling retrospective case series. The authors concluded that the ideal synthetic mesh material for pelvic surgery was yet to be developed; the

[267] ETH.MESH.02253078: Emails Re: FDA Health Notification.
[268] ETH.MESH.08003295: Patient Brochure: Treatment Options for Stress Urinary Incontinence: Stop Coping. Start Living; Significant additions were added again in 2012 to the patient brochures. See Section VII.B infra.
[269] Dr. Piet Hinoul deposition, June 27, 2013, 551:12-552:9; Axel Arnaud deposition July 19, 2013, 114:21-127:1; Catherine Beath deposition July 12, 2013, 608:13-20.
[270] Dr. Piet Hinoul deposition, June 27, 2013, 551:23-552:1.
[271] Iglesia CB, Fenner DE, and Brubaker L. The use of mesh in gynecological surgery. Int Urogynecol J 1997;8:105-115.

disadvantages of synthetic mesh included *foreign-body reaction* with the risk of *infection*, *rejection*, and *erosion*. Further, the authors commented it was likely that the rate of *graft-related complications was underestimated*, because *follow-up* of patients in most studies was *limited*. It was reported that once a vaginal erosion occurred, *removal of the mesh* might be necessary for complete healing. Due to the known complications of synthetic mesh, the authors favored autologous materials as the primary choice when technically feasible. (Emphasis added.)

Also in 1997, the American Urological Association reported the results of an analysis of the literature regarding surgical procedures for treating stress urinary incontinence. The analysis was undertaken by the Female Stress Urinary Incontinence Clinical Guidelines Panel to make practice recommendations based on treatment outcomes data.[272] Outcomes data were extracted from 282 articles considered by the panel to have some type of acceptable outcomes data, following a MEDLINE database search for all articles through 1993 on surgical treatment of female stress urinary incontinence. The panel reported that the "data indicate that after 48 months retropubic suspensions and slings appear to be more efficacious than transvaginal suspensions, and also more efficacious than anterior repairs."[273] The panel also found that "retropubic suspensions and sling procedures are associated with slightly higher complication rates, including longer convalescence and postoperative voiding dysfunction."[274] Further, "[t]he literature suggests *higher complication rates when synthetic materials are used for slings*."[275] [Emphasis added.]

Among the complications reported for sling procedures were *postoperative urgency* and *urinary retention*. "The estimated probability of temporary urinary retention lasting longer than 4 weeks [was]…..8% for sling procedures."[276] For *permanent retention*, the panel found there were no accurate data at the time of their analysis. However, "[i]n the panel's opinion the risk is somewhat higher for sling procedures than for other procedures" but "the risk of permanent retention generally does not exceed 5%," regardless of procedure.[277] Other specific complications reported included *urinary tract infection*, *vaginal erosion*, *urethral erosion*, *wound infection*, *wound sinus*, *fistula*, *seroma* (one report), and *requirement for transfusion* (4% [median value]).[278] Death was reported but noted to be a rare complication of surgery for stress urinary incontinence. For considering other complications, the following general groupings were used: general medical complications; intraoperative complications, perioperative complications; subjective complications; and complications requiring surgery. For sling procedures, rates ranged from 3-12% (median values), with a 3% rate for complications requiring surgery.[279] [Emphasis added.]

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[272] Leach GE et al. Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence. J Urology 1997;158:875-880 [included in 510(k) Number K974098 submission].
[273] *Id.*
[274] *Id.*
[275] *Id.*
[276] *Id.* at page 877.
[277] Leach GE et al. Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence. J Urology 1997;158:875-880 [included in 510(k) Number K974098 submission], at page 877.
[278] *Id.*
[279] *Id.* at pages 876-877.

In a 2001 review by Cervigni and Natale[280] of the use of synthetic mesh for repair of pelvic organ prolapse (POP), in particular, for abdominal sacral colpopexy and transvaginal cystocele, a series of properties of the 'ideal' synthetic biocompatible material was presented, including, among others, that the material should be chemically and physically inert, mechanically strong, cause no allergic or inflammatory reactions, and not be physically modified by body tissue. Importantly, none of the synthetic meshes available for use met all of the 'ideal' criteria. The most frequent mesh-related complications included the following: *infection* and *sinus tract formation*; *seroma formation* caused by *inflammatory reaction* and the dead space created between the synthetic mesh and host tissue; intestinal *adhesion*; *fistula formation*; *erosion*, which was noted to be dangerous when the mesh was in direct contact with organs without serosal covering, such as the rectum, bladder, and the denuded intestinal tract; and *mesh shrinkage* by approximately 20% due to *contraction* of the mesh fibers during the *scarring* process. *Dyspareunia* and 'de novo' *stress urinary incontinence* also were reported. Although this review assessed complications of synthetic mesh used for POP repair, instead of SUI repair, it is included here because the same mesh-related complications have also been reported for the TVT device, notably in the MAUDE database.

3.2 Clinical Evaluations Provided in 510(k) Number K974098[281]

Ulmsten et al.[282] treated 75 subjects with SUI using a modified intravaginal slingplasty procedure and followed them for two years. The only complications reported included immediate *postoperative voiding problems* necessitating an indwelling catheter over the first postoperative night in five patients (6.7%) and *urinary infection* in five patients (6.7%) within 14 days after the surgery. Otherwise, the authors reported there were "[n]o significant intra- or postoperative complications [that] occurred, i.e., no patient had bleeding >300 ml and no bladder perforation occurred."[283] Dr. Margaret Eriksson,[284] Medscand Medical, summarized the results of an open, non-randomized, prospective, multicenter study of the Ulmsten procedure with the IVS device for the treatment of SUI conducted at six medical centers in Scandinavia. Dr. Eriksson noted that this recently developed surgical procedure for SUI had been used at Akademiska sjukhuset, Uppsala and at collaborating Swedish and Scandinavian centers for some years. As of May 1997, 131 subjects had been enrolled, aged 35 to 86 years (Mean 53.08 years). Subjects were followed at 2, 6, and 12 months after surgery. Complications reported included the following: *urinary retention* (four cases that resolved within one to three days); *bladder perforation* (one case); *hematoma* (one case); and *vaginal wound infection* (one case). While three of the cases of urinary retention resolved with catheterization, the fourth required intervention. "The hematoma resolved over time

[280] Cervigni M and Natale F. The use of synthetics in the treatment of pelvic organ prolapse. Curr Opinion Urol 2001;1:429-435.
[281] As stated previously herein, all the clinical data submitted in support of the 510(k) were data from studies using the IVS device, not the actual TVT device. The studies did, however, report complications associated with the use of the device.
[282] Ulmsten U et al. An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence. Int Urogynecol J 1996;7:81-86 [included in 510(k) Number K974098 submission].
[283] *Id.* at page 84.
[284] Eriksson M (MEDSCAND). Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure - Clinical Report. October 17, 1997 [unpublished report, included in 510(k) Number K974098 submission].

without treatment while the vaginal infection required surgical intervention with resection of *exposed mesh*."[285] (Emphasis added.)

Wang and Lo[286] reported on the outcomes of 70 women with SUI who were enrolled in a non-randomized, prospective study using the Ulmsten procedure and the IVS device. . Reported complications included *bladder perforations* during surgery (3) and *blood loss > 200 ml* that necessitated an indwelling catheter and vaginal tamponade in 11 subjects (16%). Note that only a one-page study summary was available in the 510(k) submission for this study. Blaivas and Romanzi[287] reported on 28 women, aged 31-70 years, with Types 1 & 2 SUI who were treated with a pubovaginal sling, specifically, a free graft of rectus fascia, passed around the urethra and tied above the rectus fascia without tension. Subjects were followed for 1 to 6 years (mean = 1.5 years). All were cured of SUI and two developed *mild de novo detrusor instability* and one had *persistent detrusor instability*.[288] (Emphasis added.)

B. Summary: TVT Known Potential Complications

Internal Ethicon documents, testimony of Ethicon employees, and reviews of the scientific and medical literature discussed above show that the potential complications listed in Table VII.1. below were known or knowable to Ethicon to be potential risks associated with synthetic mesh for SUI repair at the time of the TVT launch or by June 2000, prior to the in-use date of the first IFU available for review (September 2000).

[285] Eriksson M (MEDSCAND). Scandinavian Multicenter Study of the Tension Free Vaginal Tape Procedure - Clinical Report. October 17, 1997 [unpublished report, included in 510(k) Number K974098 submission].
[286] Wang AC and Lo TS. Tension-Free Vaginal Tape (TVT) for Uinary Stres Incontinence --- A Preliminary Report [unpublished report, [included in 510(k) Number K974098 submission].
[287] Blaivas JG and Romanzi L. Pubovaginal Fascial Sling for Type 1 & 2 Stress Incontinence. Abstract, presented at the American Urological Association Annual Convention, 1996[included in 510(k) Number K974098 submission].
[288] *Id.*

Table VII.1. Known Potential Complications at TVT Launch (or by 2000 if so indicated)

POTENTIAL COMPLICATIONS		SOURCE
Erosion, extrusion, or exposure of mesh/rejection (may be recurrent; may require mesh removal and/or surgical treatment)		+
Pain		†
Chronic pain		†
Infection		+
Abscess		†
Fistula		+
Wound sinus		+
Seroma		+
Hematoma		+
Hemorrhage/potential requirement for transfusion		+
Venous thrombosis		†
Vaginal scarring		†
Shrinkage, due to contraction and scarring		†
Urinary problems		+
	Urethral obstruction	†
	Voiding dysfunction	+
	De novo detrusor instability or urgency	+
	Urinary retention (temporary or permanent)	+
	Urinary tract infection	+
	Dysuria	†
	Hematuria	†
	Worsening or recurrence of incontinence	†
Irritation at wound site		†
De novo dyspareunia		†
Inflammation, Inflammatory/foreign body reaction		+
Delayed healing		† (2000)
Complications requiring re-surgery		†
Complications requiring mesh removal		+
Nerve damage		†
Blood vessel perforation		†
Bowel perforation		†
Bladder perforation		+
Urethral injury		† (2000)
Vaginal perforation		† (2000)
Device failure		† (2000)
Death		+

† Known or knowable to Ethicon as evidenced from internal Ethicon documents and testimony.

+ Reported as complications in the literature for sling procedures to treat SUI and also known or knowable to Ethicon as evidenced from internal Ethicon documents and testimony.

VIII. INADEQUATE AND MISLEADING LABELING: MISBRANDING AND FAILURE TO WARN

A. Instructions for Use (IFU)

A medical device's professional labeling, namely, the Instructions for Use (IFU), is the cornerstone of risk management, because its purpose is to provide the physician with the necessary information to make decisions about device usage for a particular patient and then to use the device safely and effectively. Dr. Martin Weisberg, Medical Director at Ethicon since 2001,[289] acknowledged that the goal of the IFU is to communicate all of the most important safety risks attributable to the TVT device and, further, that an IFU should never exclude known hazards or complications related to the device or underestimate the risks of using the product.[290]

The failure of labeling to meet the requirements of the labeling regulations constitutes misbranding. Specifically, professional labeling (IFU) that contains misleading statements, has inadequate directions for use, and/or fails to warn about potential adverse consequences or contraindications for device use renders a device misbranded. Dr. Weisberg testified that the IFU fails in one of its principal purposes as regards known complications that are excluded or risks that are understated.[291] Such deficiencies in the TVT Instructions for Use are discussed below.

Based on the IFUs produced by Ethicon in this litigation, there were six versions of the TVT IFU, additional to the 1997 draft IFU included in the 510(k) submission, with the following in-use dates (first date of use shown): September 8, 2000[292]; December 22, 2003[293]; February 11, 2005[294]; April 7, 2006[295]; October 13, 2008 [296]; and November 29, 2010.[297]

For each of the six IFU versions, Table VIII.1. below shows the safety information provided in the IFU, specifically, adverse reactions, contraindications, warnings and precautions. If the information provided in these sections of the IFU is the same as the prior version, "Same as Previous" is indicated. Any differences in versions are indicated by gray shading. Notably, the adverse reactions and contraindications sections have remained exactly the same from the first use in September 2000 to the present (except for deletion of the word "polypropylene" after "PROLENE" in the contraindications section of the current in-use version, as indicated in Table VIII.1.). While three additions were made to the warnings and precautions in the second in-use version of the IFU (December 22, 2003), there have been no changes to the warnings and precautions since that time (except for inclusion of the word "Gynecare" preceding "TVT"). Yet Catherine Beath, Vice President of Quality Assurance and Regulatory Affairs, agreed that "a reasonably prudent medical device company would continually update the label consistent with developing data and

[289] Martin Weisberg, MD, deposition, August 9, 2013, 644:15-23.
[290] *Id.*, 959:19-960:16.
[291] *Id.*, 961:11-17.
[292] ETH.MESH.05225354-385: TVT Tension-free Vaginal Tape IFU, In use 09/08/2000-11/26/2003.
[293] ETH.MESH.02340306-369: Gynecare TVT Tension-free Vaginal Tape IFU, In use 12/22/2003-02/11/2005.
[294] ETH.MESH.02340471-503: Gynecare TVT Tension-free Vaginal Tape IFU, In use 2/11/2005-04/07/2006.
[295] ETH.MESH.05222673-704: Gynecare TVT Tension-free Vaginal Tape IFU, In use 04/07/2006-10/07/2008.
[296] ETH.MESH.02340504-567: Gynecare TVT Tension-free Support for Incontinence IFU, In use 10/13/2008-11/22/2010.
[297] ETH.MESH.03427878-945: Gynecare TVT Tension-free Support for Incontinence IFU, In use 11/29/2010-present.

information that becomes known to the company" when an update is appropriate.[298] Gregory Jones, former Director Regulatory Affairs at Ethicon, also testified that "it's important for medical device manufacturers, including Ethicon, to provide clear and accurate information to physicians and patients to avoid needless harms"[299] and "a medical device manufacturer should warn physicians about serious risks associated with their devices," agreeing that "it would be wrong for a medical device manufacturer not to warn of serious risks."[300]

[298] Catherine Beath deposition, July 11, 2013, 198:8-13.
[299] Gregory Jones deposition, August 20, 2013, 39:18-22.
[300] Gregory Jones deposition, August 20, 2013, 41:11-18.

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
Bates #	ETH.MESH. 05225354, 382-383	ETH.MESH. 02340306, 332-333	ETH.MESH. 02340471, 484-485	ETH.MESH. 05222673, 686-687	ETH.MESH. 02340504, 531-532	ETH.MESH. 03427878, 881-882
Dates: Brochure Date; First Use Date*; Last Use Date*	February 2000; September 8, 2000; November 26, 2003	August 2001; December 22, 2003; February 11, 2005	October 2004; February 11, 2005; April 7, 2006	October 2004; April 7, 2006; October 7, 2008	October 13, 2008; November 22, 2010	2009; November 29, 2010; Present
Adverse Reactions	Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair. Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation. As with all foreign bodies, PROLENE mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE mesh is designed to minimize the risk of contamination. Over correction i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.	Same as Previous	Same as Previous	Same as Previous	Same as Previous	Same as Previous

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
Contra-indications	As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE polypropylene mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.	Same as Previous	Same as Previous	Same as Previous	Same as Previous	As with any suspension surgery, this procedure should not be performed in pregnant patients. Additionally, because the PROLENE mesh will not stretch significantly, it should not be performed in patients with future growth potential including women with plans for future pregnancy.
Warnings and Precautions	**Do not use TVT procedure for patients who are on anticoagulation therapy. Do not use TVT procedure for patients who have a urinary tract infection.** Users should be familiar with surgical technique for bladder neck suspensions before employing the TVT device. It is however important to recognize that TVT is different from a traditional sling procedure in that the tape should be located without tension	Do not use TVT procedure for patients who are on anti-coagulation therapy. Do not use 'IVT procedure for patients who have a urinary tract infection. Users should be familiar with surgical technique for bladder neck suspensions and should be adequately trained in implanting the TVT system before employing the TVT device. It is important to	Same as Previous	Same as Previous	Do not use GYNECARE TVT procedure for patients who are on anticoagulation therapy. Do not use GYNECARE TVT procedure for patients who have a urinary tract infection. Users should be familiar with surgical technique for bladder neck suspensions and should be	Same as Previous

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
	under mid-urethra. Acceptable surgical practice should be followed for the TVT procedure as well as for the management of contaminated or infected wounds. The TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from hospital. Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley Catheter. When removing the rigid catheter guide, open the handle completely so that	recognize that TVT is different from a traditional sling procedure in that the tape should be located without tension under mid-urethra. Acceptable surgical practice should be followed for the TVT procedure as well as for the management of contaminated or infected wounds. The TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing patient from the hospital. Cytoscopy should be			adequately trained in implanting the GYNECARE TVT system before employing the GYNECARE TVT device. It is important to recognize that GYNECARE TVT is different from a traditional sling procedure in that the tape should be located without tension under mid-urethra. Acceptable surgical practice should be followed for the GYNECARE TVT procedure as well as for the management of contaminated or infected wounds. The GYNECARE TVT procedure should be performed with care to avoid large vessels, nerves, bladder and bowel. Attention to local anatomy and	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
	the catheter remains properly in place. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Post-operatively the patient is recommended to refrain from heavy lifting and/or exercise (i.e. cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria, bleeding or	preformed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley Catheter. When removing the rigid catheter guide, open the handle completely so that the catheter remains properly in place. Do not remove the plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the			proper passage of needles will minimize risks. Retropubic bleeding may occur postoperatively. Observe for any symptoms or signs before releasing the patient from the hospital. Cystoscopy should be performed to confirm bladder integrity or recognize a bladder perforation. The rigid catheter guide should be gently pushed into the Foley catheter so that the catheter guide does not extend into the holes of the Foley catheter. When removing the rigid catheter guide, open the handle completely so that the catheter remains properly in place. Do not remove the	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
	other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage to the mesh may occur. Do not resterilize TVT device. Discard opened, unused devices.	material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical experience is available with vaginal delivery following the TVT procedure, in case of pregnancy delivery via cesarean section is recommended. Post-operatively the patient is recommended to refrain from heavy lifting and/or exercise (i.e. cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria, bleeding or other			plastic sheath until the tape has been properly positioned. Ensure that the tape is placed with minimal tension under mid-urethra. PROLENE Mesh in contaminated areas should be used with the understanding that subsequent infection may require removal of the material. The patient should be counseled that future pregnancies may negate the effects of the surgical procedure and the patient may again become incontinent. Since no clinical experience is available with vaginal delivery following the GYNECARE TVT procedure, in case of pregnancy delivery via cesarean section	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
		problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be corroded should not be used and should be discarded. As with other incontinence procedures, de novo detrusor instability may occur following the TVT procedure. To minimize this risk, make sure to place the tape tension-free in the mid-urethral position. Do not contact the PROLENE mesh with any staples, clips or clamps as mechanical damage			is recommended. Postoperatively, the patient is recommended to refrain from heavy lifting and/or exercise (i.e., cycling, jogging) for at least three to four weeks and intercourse for one month. The patient can return to other normal activity after one or two weeks. Should dysuria , bleeding or other problems occur, the patient is instructed to contact the surgeon immediately. All surgical instruments are subject to wear and damage under normal use. Before use, the instrument should be visually inspected. Defective instruments or instruments that appear to be	

TABLE VIII.1. TVT INSTRUCTIONS FOR USE (IFU)

***Shaded areas indicate that a change in wording was made from the previous version.**

Product	TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Vaginal Tape	Gynecare TVT Tension-free Support for Incontinence	Gynecare TVT Tension-free Support for Incontinence
		to the mesh may occur. Do not resterilize TVT device. Discard opened, unused devices.			corroded should not be used and should be discarded. As with other incontinence procedures, de novo detrusor instability may occur following the GYNECARE TVT procedure. To minimize this risk, make sure to place the tape tension-free in the mid-urethral position. Do not contact the PROLENE Mesh with any staples, dips or clamps, as mechanical damage to the mesh may occur. Do not resterilize GYNECARE TVT device. Discard opened, unused devices	

*Date provided by attorneys

1. Safety Information Missing from IFUs: Adverse Reactions

The "Adverse Reactions" section of medical device labeling should include all adverse reactions, or undesirable effects, reasonably associated with the use of the device, including those that are also mentioned in the "Contraindications," "Warnings," and "Precautions" sections of the labeling. As appropriate, the listing of adverse reactions should be followed by statement(s) that direct the reader to other section(s) of the labeling (e.g., Warnings) for additional information and steps to be taken in regards to the adverse reactions. Adverse reactions should be listed in the labeling according to their clinical significance, i.e., those occurring with greater severity and frequency should be listed first.[301]

From the time of launch of the TVT, the adverse reactions listed below were known or knowable to Ethicon, as discussed previously in this Report, yet were missing from the IFU. As a result, surgeons were denied both the full scope of safety information necessary to assess the potential risks of implanting the device, versus the benefit, and also information concerning potential and known adverse reactions for which patients should be monitored and managed during and after implantation. Moreover, surgeons lacked the necessary information to fully inform and consent patients regarding the potential risks of TVT implantation. As Catherine Beath, Ethicon's Vice President of Quality Assurance and Regulatory Affairs, confirmed, "physicians should be made aware of all the significant safety risks associated with the product in the IFU."[302] Medical Director Dr. Robinson also agreed that it is "important for patient safety to have all the significant risks and complications be provided to both doctors and to patients either from doctors or from information from the company."[303] According to Medical Director Dr. Martin Weisberg, Ethicon's "policy is to include any adverse events related to the device that are expected to happen on a more than occasional basis."[304] Ethicon failed to comply with that policy and fell below the standard of care required of a reasonably prudent medical device manufacturer by its failure to warn physicians of the following risks:

- Pain, including chronic pain
- Infection (Only "may potentiate an *existing* infection" is included.) (Emphasis added.)
- Abscess
- Wound sinus
- Seroma
- Hematoma
- Hemorrhage (Note that the Warnings and Precautions, however, include that "[r]etropubic bleeding may occur postoperatively" and that if bleeding should occur, "the patient is instructed to contact the surgeon immediately.")
- Venous thrombosis
- Vaginal perforation
- Vaginal scarring
- Foreign body reaction

[301] Device Labeling Guidance 3/8/91 [G91-1] – Blue Book Memo.
[302] Catherine Beath deposition, July 12, 2013, 592:7-11.
[303] Dr. David Robinson deposition (rough transcript), September 11, 2013, 240:3-8.
[304] Dr. Martin Weisberg deposition, August 9, 2013, 707:19-24.

- Delayed healing
- Shrinkage, due to contraction and scarring
- Urinary problems, including:
  - Urethral injury
  - Voiding dysfunction
  - De novo detrusor instability or urgency (Note that in the IFUs in-use from 12/22/2003, the Warnings and Precautions included that "de novo detrusor instability may occur following the TVT procedure.")
  - Urinary retention
  - Urinary tract infection
  - Dysuria (Note that the Warnings and Precautions include that if dysuria should occur, "the patient is instructed to contact the surgeon immediately.")
  - Hematuria
  - Worsening or recurrence of incontinence
- De novo dyspareunia
- Complications requiring mesh removal and/or re-operation
- Device failure
- Death (Note that 15 deaths have been reported in the MAUDE database).

2. Safety Information Missing from IFUs: Warnings and Precautions

Serious adverse reactions such as those that may result in a persistent or significant incapacity or have the potential to substantially disrupt a patient's ability to conduct normal life functions should be described in the Warnings section of the labeling, in addition to those that may require medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Other clinically significant adverse reactions, e.g., those that occur frequently and have implications for patient management or may lead to a potentially serious outcome, also should be included in the Warnings section. As applicable, the description of an adverse reaction in the Warnings section also should include actions to be taken to reduce the likelihood or severity of the event and how to monitor for or manage the event.

The Warnings in the TVT IFUs from the first in-use IFU through the IFU in current use have been and are now incomplete in my professional opinion. In my professional opinion, the Warnings listed below (or similar wording) should have been included in all IFUs.

- Mesh extrusion or erosion may occur and is a persistent or lifelong risk; some will require surgical correction, and multiple surgeries may be necessary. There is the potential risk that a patient may experience chronic, unresolvable pain.
  - Dr. David Robinson testified that there is a risk of erosion "as long as the foreign body remains in place." While the IFU included erosion and extrusion as adverse reactions, there was no warning that such risk was lifelong or that patients could have multiple erosions requiring multiple surgeries, yet this was known. Further, he acknowledged that in such cases the patient's pain might never be resolved.[305]
- De novo dyspareunia may occur and be persistent.

[305] Dr. David Robinson deposition (rough transcript), September 11, 2013, 328:11-21; 329:12-330:7.

  - Dr. Robinson acknowledged the occurrence of dyspareunia (painful sexual intercourse) and that this warning does not appear in the IFU.[306]
- Erosion through the vaginal mucosa may cause irritation to the patient's intimate partner.
- The TVT is intended to be a permanent implant, but foreign body reaction and inflammation may require implant removal; complete removal may not be possible, and morbidity associated with explant may be significant.
  - Dr. Robinson agreed that he "knew at all times while [he was] the medical director, that there would be a foreign body reaction any time the mesh would go in the woman's body."[307] As long as mesh is still present, "there will be some long-term foreign body reaction to it or reaction."[308] Yet, as Dr. Robinson further testified, the IFU states only that "a transitory foreign body response may occur" (in the adverse reactions section of the IFU).[309] As Dr. Piet Hinoul testified, if complications such as chronic pain, dyspareunia, or other complication necessitate mesh removal, the removal "can prove to be a challenge" because of tissue in-growth, and there can be "damage to tissue during the removal process or other complications related to the removal surgery."[310]
- Chronic pain may result from foreign body reaction and/or scarring and contraction.
  - Dr. Robinson affirmed that Ethicon "was getting complaints related to chronic pelvic pain" and that he knew there were related data in the literature.[311] He acknowledged that "when mesh contracts, that can cause pain for patients."[312] Importantly, the extent of contraction or shrinkage is related to the intensity of the foreign body reaction; excessive foreign body reaction results in a massive scar plate and, thus, more shrinkage. There are differences among individual patients regarding the extent of foreign body reaction, i.e., there are "high and low responders."[313]
- TVT mesh has been reported to narrow, curl or deform with tension which may lead to erosion or pain for patients. Loss of pore size due to mesh narrowing or deformation may also lead to urinary retention or erosion.[314]
- TVT mesh was shown to be cytotoxic in some in vitro tests for cytotoxicity.
- The polypropylene used in the TVT mesh gave rise to local sarcomas in a study in which it was implanted in rats.

B. Patient Brochure (Patient Labeling)

A Patient Brochure was not included for FDA's review in the "Proposed Labeling" section of the initial 510(k) Premarket Notification for the TVT (K974098) nor in the subsequent 510(k)

[306] *Id.*, 330:20-331:20.
[307] Dr. David Robinson deposition (rough transcript), September 11, 2013, 275:21-25.
[308] *Id.*, 277:5-12.
[309] *Id.*, 280:5-11.
[310] *Id.*, 578:12-579:4.
[311] *Id.*, 172:18-173:3.
[312] *Id.*, 270:6-10.
[313] Powerpoint: Factors related to mesh shrinkage: What do we know? A review of literature and internal studies, by K. Spychaj, 02/23/2007 (Exhibit No. 1286, Dr. David Robinson deposition, 09/11/2013).
[314] ETH.MESH.01218019: Design FMEA TVT LCM Project; David Robinson deposition, September 11, 2013, 1079:3-7; 1081:9-13; 1083: 8-18.

submission (K012628). The information that is required in a premarket notification submission includes "Proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use."[315] The date printed on the first Patient Brochure available for review is 2001. Notably, K012628 was submitted to the FDA in August 2001 and cleared October 26, 2001.

Patient labeling is defined as any information associated with a device that is targeted to the patient (or lay caregiver), including brochures or leaflets given to and used by patients with or without accompanying professional counseling,[316] and includes Brochures on the manufacturer's website. The two general categories of information in patient labeling are risk/benefit information and instructions for use. For implants such as the TVT device, patient labeling generally consists of risk/benefit information to help patients decide whether to have a device used on them and to allow patients to become aware of potential problems with the device. Patient labeling may also include descriptive information about the device, types of patients for whom the device would not be a good choice, alternative therapeutic choices, and any other information to enable the person to make an informed decision about the device.[317] Such information is particularly important for patients with non-life-threatening conditions such as stress urinary incontinence, which, as Dr. David Robinson, Ethicon Medical Director,[318] testified is primarily a quality of life issue.[319]

In the documents available for my review, there were 14 Patient Brochures (final copy) with the following dates: 2001 (one)[320]; 2004 (one)[321]; 2005 (one)[322]; 2006 (two)[323,324]; 2007 (two)[325,326]; 2008 (two)[327,328]; 2009 (one)[329]; 2010 (two)[330,331]; 2011 (one)[332]; and 2012 (one)[333]. I also reviewed a patient video presently on the Gynecare TVT Retropubic System website. Exhibit 2 provides the risks and safety information presented in each Brochure and notes any change(s) from previous version(s).

In my professional opinion, the TVT Brochures display multiple labeling issues. First, as discussed above regarding the IFUs, many potential risks known or knowable to Ethicon were missing from

[315] 21 CFR § 807.87(e).
[316] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[317] *Id.*
[318] Dr David Robinson deposition September 11, 2013, 936:20-23.
[319] *Id.*, 132:7-10.
[320] ETH.MESH.08003173-180: GYNECARE TVT Patient Brochure 2001.
[321] ETH.MESH.08003181-196: GYNECARE TVT Patient Brochure 2004.
[322] ETH.MESH.08003197-212: GYNECARE TVT Patient Brochure 2005.
[323] ETH.MESH.08003231-246: GYNECARE TVT Family of Products Patient Brochure 2006.
[324] ETH.MESH.08003215-230: GYNECARE TVT Family of Products Patient Brochure 2006.
[325] ETH.MESH.08003247-262: GYNECARE TVT Family of Products Patient Brochure 2007.
[326] ETH.MESH.08003263-278: GYNECARE TVT Patient Brochure 2007.
[327] ETH.MESH.03458123-138: GYNECARE TVT Family of Products Patient Brochure 2008.
[328] ETH.MESH.08003279-294: GYNECARE TVT Family of Products Patient Brochure 2008.
[329] ETH.MESH.08003303-318: GYNECARE TVT Family of Products Patient Brochure 2009.
[330] ETH.MESH.06087471-472: GYNECARE TVT Patient Brochure 2010.
[331] ETH.MESH.06087513-514: GYNECARE TVT Patient Brochure 2010.
[332] ETH.MESH.08003295-302: GYNECARE TVT Family of Products Patient Brochure 2011.
[333] ETH.MESH.05815791-802: GYNECARE TVT Family of Products Patient Brochure 2012.

the Patient Brochures, although all Brochures included a section about "What are the risks," except for the two 2010 Patient Brochures. The latter were a different style (one-page, two-sided) and appear to have been designed simply to raise awareness about the TVT device and elicit interest, whereas all the other Brochures provided substantial information, for example, information on stress urinary incontinence, treatment options, how TVT differs from other options, etc. Except for the 2012 Brochure, all "What are the risks" sections began with a statement that all surgical (or medical) procedures present risks (or some risks). Table VIII.2. below shows the risk information provided in each Brochure.

Note that attached to or included with all Brochures was product safety information (adverse reactions, warnings and precautions, and/or contraindications) that was substantially the same as or an abbreviated version of the information in the professional labeling (package insert/IFU). Such product information included material that (i) is relevant only to the surgeon and not to the patient, (ii) is written in technical language that the lay patient would not be expected to understand, and (iii) is in a much smaller print size than the print used for the remainder of the Brochure, which downplays its significance. In my professional opinion, the presentation of this information did not accomplish the purpose of patient labeling, which is to provide information on the proper use, risks, and benefits of the device in language the patient can understand. Ethicon agrees with my opinion in this regard as Susan Lin, Ethicon's designated regulatory corporate representative, testified that the product information attached to the brochures was not intended for patients and was not written in lay language that could be understood by patients.[334] Yet, there appears to have been no attempt to translate the information in the professional labeling of relevance to the patient into layman's language. Nor was the safety information complete, as has been discussed above regarding the IFUs. Yet all Patient Brochures through 2009 instructed the patient to see the attached product information for a "complete description of risks."

[334] Susan Lin deposition, May 2, 2013 687:25-689:2

Table VIII.2. Risk Information Included in Patient Brochures: 2001-2012

Patient Brochure Date of Printing	Risks Provided
2001	Complications rare - Injury to blood vessels of pelvic sidewall and abdominal wall - Difficulty urinating - Bladder and bowel injury
2004	Same as 2001
2005	Same as 2001
2006 ETH.MESH.08003231 at 244	As with all procedures of its type - Risk of injury to bladder and surrounding organs
2006 ETH.MESH.08003215at 228	Same as other 2006 Brochure
2007 ETH.MESH.08003247 at 260	Same as 2006
2007 ETH.MESH.08003263 at 276	Same as 2006
2008 ETH.MESH.03458123 at 136	Same as 2006
2008 ETH.MESH.08003279 at 292	- Injury to blood vessels of the pelvis - Difficulty urinating - Pain - Scarring - Pain with intercourse - Bladder and bowel injury - Risk of mesh material becoming exposed, requiring treatment
2009	Same as 2008 (ETH.MESH.08003279 at 292)
2011	- Injury to blood vessels of the pelvis - Nerve damage - Difficulty urinating - Pain with intercourse - Bladder or bowel injury - Risk of mesh material becoming exposed into the vaginal canal -- Can be associated with pain during intercourse for patient and her partner -- May require treatment such as vaginal medication or removal of exposed mesh, either in office or operating room - Synthetic mesh is a permanent medical device implant. -- Carefully discuss decision to have surgery with your doctor. -- Understand benefits and risks of mesh implant surgery before deciding how to treat your condition.

Table VIII.2. Risk Information Included in Patient Brochures: 2001-2012 (contd.)

Patient Brochure Date of Printing	Risks Provided
2012	Risks Common to All Pelvic Surgeries: - Pain with intercourse - Pelvic pain - Development of urinary incontinence or voiding difficulties - Hemorrhage (bleeding) or hematoma (collections of blood in the pelvis) - Injury to abdominal organs including bowel - Urinary tract infection - Bladder injury - Wound healing problems - Fistula (holes between bladder or bowel and the vagina) - Injury to ureters (tubes bringing urine from kidneys to bladder) - Pelvic abscess formation - Nerve damage Complications Associated with Synthetic Mesh: - Risk of mesh material becoming exposed into the vagina -- Can be associated with pain during intercourse for patient and her partner -- May require treatment such as vaginal medication or removal of exposed mesh, either in office or operating room - Infection - Inflammation - Vaginal scarring and mesh contracture (mesh shortening due to scar tissue) - Pelvic pain (may occur and may resolve with time) - Pain with intercourse (may occur and may resolve with time) - Urinary incontinence - Difficulty urinating - Synthetic mesh is a permanent medical device implant. -- Carefully discuss decision to have surgery with your doctor. -- Understand benefits and risks of mesh implant surgery before deciding how to treat your condition.

The above table shows that it was not until 2012 that the Patient Brochure informed patients of the majority of potential risks of TVT implantation, yet all these risks were known or knowable to Ethicon at the time of product launch, as discussed above and delineated in Table VII.1. Still in 2012, there were missing risks, including the following: irritation at the wound site, wound sinus, seroma; additional urinary problems, including hematuria, urethral injury or obstruction, urgency, temporary or permanent urinary retention; vaginal perforation; blood vessel perforation [notably, included in the 2001, 2004, 2005, 2008 (one of two), 2009, and 2011 Brochures]; venous thrombosis; complications additional to mesh exposure that might require mesh removal and/or surgical correction; death, e.g., in the event of bowel perforation. Prior to 2012, the Patient

Brochures informed patients of as few as 3% and no more than approximately 20% of the known or knowable risks at the time of TVT launch, according to the information provided in Table VII.1. Although Brochures began advising patients that the mesh is a permanent implant from 2008 (one of two 2008 Brochures[335]) and thus the patient "should carefully discuss the decision to have surgery with [her] doctor and understand the benefits and risks of mesh implant surgery before deciding how to treat [her] condition,"[336] no Brochure ever communicated that surgery to remove the mesh, if necessary because of complications, might prove challenging as a result of tissue in-growth and could cause significant morbidity. While referring the patient to her doctor for discussion of benefits and risks was appropriate, it does not replace also including known potential complications and consequences of TVT device implantation in the Brochure. Moreover, as discussed above regarding the IFU, the safety information provided in the professional labeling was incomplete and failed to provide the physician with all the necessary information to conduct a fully informed discussion of the product benefits and risks with the patient.

Additionally, the TVT Patient Brochures lacked fair balance. Risk and benefit information is to be presented in a balanced way in patient labeling and is intended to inform without any attempt to influence the patient.[337] The overriding message of the Brochures is first defined by their tag lines:

- Freedom From Stress Urinary Incontinence - It's within your control.[338]
- Stress Urinary Incontinence in Women – What YOU can do about it…[339,340]
- The Choice to End Stress Urinary Incontinence – Find out how to stop urine leakage like Bonnie did[341,342,343,344]
- The Choice to End Stress Urinary Incontinence – **One day** you have urine leakage. The next day you don't. **End of story.**[345]
- Treatment Options for Stress Urinary Incontinence – Stop coping. Start living.[346,347,348]
- Stress Urinary Incontinence - Stop coping. Start living.[349]
- Stop Coping. **Start Living**. What You Should Know About **Stress Urinary Incontinence.**[350]

Additionally, in each of the Brochures (except the two 2010 Brochures), there are five to eight photos depicting women as happy, active, and smiling with a male partner or friends, and an

[335] ETH.MESH.08003279 at 292: GYNECARE TVT Family of Products Patient Brochure 2008.
[336] *Id.*
[337] Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers. Document issued on: April 19, 2001.
[338] ETH.MESH.08003173: GYNECARE TVT Patient Brochure 2001.
[339] ETH.MESH.08003181: GYNECARE TVT Patient Brochure 2004.
[340] ETH.MESH.08003197: GYNECARE TVT Patient Brochure 2005.
[341] ETH.MESH.08003231: GYNECARE TVT Family of Products Patient Brochure 2006.
[342] ETH.MESH.08003215: GYNECARE TVT Family of Products Patient Brochure 2006.
[343] ETH.MESH.08003247: GYNECARE TVT Family of Products Patient Brochure 2007.
[344] ETH.MESH.03458123: GYNECARE TVT Family of Products Patient Brochure 2008.
[345] ETH.MESH.08003263: GYNECARE TVT Patient Brochure 2007.
[346] ETH.MESH.08003279: GYNECARE TVT Family of Products Patient Brochure 2008.
[347] ETH.MESH.08003303: GYNECARE TVT Family of Products Patient Brochure 2009.
[348] ETH.MESH.08003295: GYNECARE TVT Family of Products Patient Brochure 2011.
[349] ETH.MESH.06087471: GYNECARE TVT Patient Brochure 2010.
[350] ETH.MESH.05815791: GYNECARE TVT Family of Products Patient Brochure 2012.

engaged physician. There are multiple benefit messages about the TVT or TVT family of products, particularly noticeable beginning with the 2004 version, which includes the messages shown below:

- Safe and effective minimally invasive procedures…[351]
- Most reliable, permanent results[352]
- Simpler, much less invasive than traditional surgical procedures…[353]
- …*take the next step* and talk with your doctor or other healthcare professional[354] (Emphasis added.)
- Innovative, minimally invasive 30-minute, outpatient treatment
- Proven results for the effective treatment of stress urinary incontinence[355]
- Clinically proven, safe and effective[356]
- Permanent material that will be well tolerated by your body[357]
- It will be there to help support your urethra for the rest of your life[358]
- Very little or no discomfort after the procedure[359]

By contrast, only after all the above positive messages have been presented is there a single, 6-line paragraph on risks that advises the patient that all medical procedures present risks and lists a few complications, after stating they are rare.

Subsequent Brochures communicated the same or similar multiple benefit messages as those listed above, including also such messages as the following:

- Only treatment of its type with demonstrated long-term (or the longest term) clinical results – clinically proven, safe and effective[360,361]
- Only procedure of its type with 7 years of proven results – clinically proven, safe and effective[362]
- 98% of women treated with GYNECARE TVT are still dry or report significantly less leakage seven years after treatment[363,364,365,366]

[351] ETH.MESH.08003181at 183: GYNECARE TVT Patient Brochure 2004.
[352] *Id.*
[353] *Id.*
[354] ETH.MESH.08003181at 187: *Id.*
[355] ETH.MESH.08003181at 190: *Id.*
[356] ETH.MESH.08003181at 191: *Id.*
[357] ETH.MESH.08003181at 192: *Id.*
[358] ETH.MESH.08003181at 192: *Id.*
[359] ETH.MESH.08003181at 194: *Id.*
[360] ETH.MESH.08003215 at 216: GYNECARE TVT Family of Products Patient Brochure 2006.
[361] ETH.MESH.03458123 at 133: GYNECARE TVT Family of Products Patient Brochure 2008.
[362] ETH.MESH.03458123 at 124: *Id.*
[363] ETH.MESH.08003215 at 216, 225: GYNECARE TVT Family of Products Patient Brochure 2006.
[364] ETH.MESH.08003231 at 232, 241: GYNECARE TVT Family of Products Patient Brochure 2006.
[365] ETH.MESH.08003247 at 248: GYNECARE TVT Family of Products Patient Brochure 2007.
[366] ETH.MESH.03458123 at 124, 133: GYNECARE TVT Family of Products Patient Brochure 2008.

- 97% of women surveyed following treatment with GYNECARE TVT™ were still dry or had significantly less leakage 11 years later! These women were so satisfied…that 97% said they would recommend the procedure with GYNECARE TVT™ to a friend[367,368]
- Demonstrated proven results for effectively treating stress urinary incontinence for over 11 years[369]
- Used on (or used to treat) more than 1 million women worldwide, more than any other treatment of its type[370,371,372]
- With over 1.5 million women treated worldwide, GYNECARE TVT™ is clinically proven safe and effective[373]
- Recovery is quick….back to your normal routine in just a day or two[374] or back to regular routine shortly[375]
- GYNECARE TVT…stop[s] urine leakage the way your body was designed to…[376,377,378] or designed to stop involuntary leakage the way your body should[379] or normally should[380]
- Rate of complications with GYNECARE TVT is very low[381,382]
- Rate of complications is low and most patients expect a short recovery period[383,384]
- …GYNECARE TVT, the #1 doctor-preferred treatment of its type[385]
- You don't have to suffer with it. Use this brochure to…learn about safe, effective, minimally invasive treatments[386]
- Minimal or no (or minimal) scarring and should not feel the mesh once it has been placed[387,388]
- …there are treatments that could reduce urine leakage or stop it altogether, so you can get back to doing the things you enjoy most[389]
- **All mesh is NOT created equal.** GYNECARE TVT™ is the most commonly studied procedure using mesh for SUI repair; and a substantial number of clinical trials have been published…..proven evidence of safety and effectiveness[390]

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[367] ETH.MESH.08003279 at 291: GYNECARE TVT Family of Products Patient Brochure 2008.
[368] ETH.MESH.08003303 at 315: GYNECARE TVT Family of Products Patient Brochure 2009.
[369] ETH.MESH.05815791 at 796: GYNECARE TVT Family of Products Patient Brochure 2012.
[370] ETH.MESH.08003215 at 216: GYNECARE TVT Family of Products Patient Brochure 2006.
[371] ETH.MESH.08003247 at 248: GYNECARE TVT Family of Products Patient Brochure 2007.
[372] ETH.MESH.03458123 at 124: GYNECARE TVT Family of Products Patient Brochure 2008.
[373] ETH.MESH.08003295 at 301: GYNECARE TVT Family of Products Patient Brochure 2011.
[374] ETH.MESH.08003215 at 225: *Id.*
[375] ETH.MESH.03458123 at 133: GYNECARE TVT Family of Products Patient Brochure 2008.
[376] ETH.MESH.08003215 at 226: *Id.*
[377] ETH.MESH.08003279 at 288: GYNECARE TVT Family of Products Patient Brochure 2008.
[378] ETH.MESH.08003303 at 312: GYNECARE TVT Family of Products Patient Brochure 2009.
[379] ETH.MESH.08003295 at 300: GYNECARE TVT Family of Products Patient Brochure 2011.
[380] ETH.MESH.05815791 at 798: GYNECARE TVT Family of Products Patient Brochure 2012.
[381] *Id.*
[382] ETH.MESH.08003231 at 242: GYNECARE TVT Family of Products Patient Brochure 2006.
[383] ETH.MESH.08003279 at 291: GYNECARE TVT Family of Products Patient Brochure 2008.
[384] ETH.MESH.08003303 at 315: GYNECARE TVT Family of Products Patient Brochure 2009.
[385] ETH.MESH.08003215 at 228: GYNECARE TVT Family of Products Patient Brochure 2006.
[386] ETH.MESH.03458123 at 125: GYNECARE TVT Family of Products Patient Brochure 2008.
[387] ETH.MESH.08003295 at 300: GYNECARE TVT Family of Products Patient Brochure 2011.
[388] ETH.MESH.05815791 at 800: GYNECARE TVT Family of Products Patient Brochure 2012.
[389] ETH.MESH.05815791 at 792: GYNECARE TVT Family of Products Patient Brochure 2012.
[390] ETH.MESH.05815791 at 797: GYNECARE TVT Family of Products Patient Brochure 2012.

- **Gynecare TVT™ is the gold standard in suburethral slings**
  - Studied in more women than other suburethral slings on the market
  - Studied longer than any other sling in the market
  - 97% of women experience little or no leakage…
  - More than 2 million patients have been treated worldwide[391]

Importantly, such statements in the Brochures that "98% of women treated are still dry or report significantly less leakage seven years after treatment" and "97% of women experience little or no leakage…" are misleading. As presented, these statements imply that Ethicon has outcome information for all women implanted with the TVT device, yet the source of this percentage is the seven-year follow-up of patients enrolled in the original Ulmsten et al. 1996 study.[392,393] Thus, these statements are based on clinical evaluation of only 64 women and telephone evaluation of another 16, for a total of only 80 women on which such global statements are based. It is further important to note that these statements are followed by a statement that TVT has been used to treat more than 1 million women worldwide, thus giving the appearance to the reader that 980,000 women have been successfully treated with TVT. There is no mention of such studies as the Ward and Hilton prospective multicenter evaluation[394] of the TVT versus colposuspension, in which 175 patients randomized to TVT treatment showed an objective cure of *66%* or the Barber et al. study[395] in which *79%* of 88 patients randomized to TVT (versus 82 patients randomized to transobturator tape) reported their bladder symptoms were either "much better" or "very much better" one year after study. (Emphasis added.)

Additionally, such statements as "[r]ate of complications with GYNECARE TVT is very low," or low, are misleading. For example, Jeffrey et al.[396] retrospectively evaluated 112 consecutive women treated with the TVT procedure at a single hospital in Paris in February 2000 and found that 32.1% experienced early postoperative complications, including the following: voiding difficulties lasting > 15 days (12.5%); urinary infection (10.7%); urinary retention (8%). Late postoperative complications occurred in 29.4% of patients, including de novo urge symptoms (25.9%) and voiding difficulties lasting > 15 days (3.6%). Bodelsson et al.[397] reported perioperative bladder or urethral perforation in 26 (15%) of 177 patients who underwent the TVT procedure at Malmo University Hospital, Sweden. Karram et al.[398] reported 19 bladder perforations in 17 (4.9%) of 350 consecutive patients treated with the TVT by one surgeon at Good Samaritan Hospital, University of Cincinnati Medical School from November 1997 to November 2001. Abouassaly et al. reported complications of TVT surgery based on a retrospective multi-

[391] ETH.MESH.05815791 at 798: GYNECARE TVT Family of Products Patient Brochure 2012.
[392] Ulmsten U et al. An ambulatory surgical procedure under local anesthetic for treatment of female urinary incontinence. Int Urogynecol J 1996;7:81-86.
[393] Dr. David Robinson deposition (rough transcript), September 11, 2013, 208:10-22.
[394] Ward K and Hilton P. Prospective multicentre randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002;325:1-7.
[395] Barber MD et al. Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence. Obstet Gynecol 2008;111:611-621.
[396] Jeffry L et al. Objective and subjective cure rates after tension-free vaginal tape for treatment of urinary incontinence. Urology 2001;58:702-706.
[397] Bodelsson G et al. Short term complications of the tension free vaginal tape operation for stress urinary incontinence in women. BJOG 2002;109:566-569.
[398] Karram MM et al. Complications and untoward effects of the tension-free vaginal tape procedure. Obstet Gynecol 2003;101:929-932.

institutional review performed by a single urologist of 241 patients at six hospitals (two university and four community hospitals). Among the complications were blood loss > 250 mL (13 patients, 5.4%) and bladder perforation (14 patients, 5.8%) intraoperatively. Post-surgical complications included urinary retention in 47 patients (19.5%): < 48 hours – 32 patients; > 48 hours – 15 patients. Of the patients with long-term retention, seven required TVT release and three required sectioning of the TVT [10 patients total (4.1%) requiring TVT release or sectioning]. At the one-year follow-up, there were 33 cases (13.6%) of de novo urge and 15 (6.2%) patients with mild but persistent suprapubic discomfort and 25 (10.4%) who reported at least one urinary tract infection within three months after surgery. As discussed above, Barber et al.[399] randomized 170 patients to treatment with TVT (88 patients) or transobturator tape (82 patients) to test the hypothesis that the latter approach, the purpose of which was to reduce the risk of bladder, bowel and iliac vessel injury, is not inferior to TVT. The authors note that despite its proven efficacy, the TVT is associated with rare but serious, and in some cases life-threatening, complications and is associated with a 3-9% bladder perforation rate. Study complications included, among others, mesh erosions in five (5.7%) TVT patients and abnormal bladder function (incontinence symptoms of any type; positive cough stress test; retreatment for SUI; or postoperative urinary retention) in 46.6% of TVT patients. New or worsening urge incontinence was noted after surgery in 10% of the TVT group. Rates of complications cited in these publications show that it was misleading to tell prospective patients that rate of complications is very low (or low). Even today, the patient video currently on the TVT Retropubic System website informs prospective patients that complications are rare.

For the reasons stated, the Patient Brochures failed to convey a true overview of the risks versus the benefits. Thus, the TVT Brochures failed to serve the expected intent of patient labeling, i.e., to provide factual and balanced information to aid the patient in deciding whether to have the device implanted or to select an alternative course of SUI management. The patient labeling conveyed a false and misleading impression by its failure to inform the patients of relevant information and potential risks and consequences of TVT implantation. Under Section 502 of the FDCA, this constituted misbranding. In my professional opinion, the TVT Patient Brochures fell below the industry standard of care.

Additionally, the 2012 Brochure constituted misbranding, in my professional opinion, as a result of conveying an impression of official FDA approval of the TVT device. Specifically, the Brochure noted that the patient "may be aware that in 2011 the FDA issued a safety communication concerning complications associated with surgical mesh used for pelvic organ prolapse repair." The patient was advised that "[m]esh used for pelvic organ prolapse repair is a different procedure than the mesh used to treat SUI. One type of SUI treatment is getting further scrutiny from the FDA, which is single incision slings. It is a different procedure that those used for GYNECARE TVT™ Retropubic…" The statement that constitutes misbranding followed next: "GYNECARE TVT™ Retropubic….[is] used to treat SUI, and the safety and efficacy of [this device] met the criteria for retropubic…slings established by the FDA."[400] According to 21 CFR 807.97, "[a]ny representation that creates an impression of official approval of a device because of complying with the premarket notification regulations is misleading and constitutes misbranding."

[399] Barber MD et al. Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence. Obstet Gynecol 2008;111:611-621.
[400] ETH.MESH.05815791 at 797: GYNECARE TVT Family of Products Patient Brochure 2012.

It is the manufacturer's responsibility to ensure that professional labeling and patient labeling are consistent. My review of the IFUs and Patient Brochures, as discussed above, shows there was never complete consistency between these two forms of labeling. Ethicon significantly improved the risk information in the 2012 Patient Brochure, after having made some improvements beginning in 2008. It is notable that the risk information in the 2012 Brochure generally exceeded the risk information in the IFU, yet there remained information in the IFU that was not included in the 2012 Patient Brochure as well as vice versa. Both professional and patient labeling remained deficient as regards failure to warn of all potential known or knowable risks. It is further noteworthy that the risk of pain, vaginal scarring and shrinkage due to scarring and contraction, dyspareunia, incontinence, voiding dysfunction, urinary tract infection, abscess and wound healing appeared in the 2012 Patient Brochure but never appeared in the IFU, including the one in current use.

OPINION #2: TVT System Misbranded Due to Failure to Warn

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively. While labeling for prescription devices is premised on the concept that prescription devices are not safe for use except under the supervision of a licensed practitioner and, accordingly, are exempt from the "adequate directions for use" requirements applicable to over-the-counter (OTC) devices,[401] prescription device labeling nevertheless is required to contain information adequate for a licensed practitioner to use the device safely and effectively for its intended use.[402] Required use information includes indications, effects, routes, methods, and any relevant hazards, contraindications, side effects, and precautions under which the device can be used safely.[403]

Ethicon marketed the TVT System without adequate instructions for use, in particular, without adequate warnings and information about potential risks, throughout the life of the product, based on my review of the TVT IFU and patient labeling information discussed above. As the testimony of Ethicon employees and documentation and information discussed in this Report demonstrate, the company knew or should have known of the above-discussed multiple risks associated with the TVT System that were not included in the IFU and patient labeling information. Nor did the patient labeling show fair balance of benefit vs. risk information. Section 502 of the FDCA contains provisions on misbranding and the labeling issues that cause a product to be misbranded. Labeling issues that cause a device to be misbranded include labeling that is false or misleading in any particular[404] and labeling that does not bear adequate directions for use, including adequate warnings.[405] In my professional opinion, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing a product that was misbranded because of the stated multiple labeling deficiencies.

[401] 21 CFR § 801.109.
[402] 21 CFR § 801.109(c).
[403] 21 CFR § 801.109(d).
[404] FDCA § 502(a), 21 U.S.C. § 352(a).
[405] FDCA § 502(f)(2).

C. Promotional Labeling

Promotional labeling is generally considered any labeling other than the professional labeling or FDA-approved labeling. Such labeling must not be false or misleading or omit material information. Following is a discussion of representative examples of promotional pieces that were false and misleading and failed to present material facts. They constituted misbranding and also reflect an absence of concern for patient safety. Notably, in determining whether labeling is misleading, "there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling…fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling….relates under the conditions of use prescribed in the labeling…thereof or under such conditions of use as are customary or usual."[406]

1. "5 Years of Proven Performance" Marketing Piece

Ethicon developed and provided this TVT marketing piece, titled "5 Years of Proven Performance," to physicians for them to see the five-year results of the Ulmsten/Nilsson study.[407] It is misleading in a number of ways. For example, physicians are not informed that the sling used in this study with five years of follow up was the IVS device and not the actual TVT device. Further, there is not a statement anywhere in the marketing piece that identifies the conflict of interest that Professor Ulmsten and Professor Nilsson have due to the fact that Professor Ulmsten was paid millions of dollars by Ethicon (including that the company he was an owner of was paid if, and only if, it could product positive safety results in a study) and Professor Nilsson was paid a substantial amount as a consultant as well.[408] In addition, this marketing piece reports that the "Urethral erosion rate $\leq$ that of traditional slings" and cites a publication which, according to the bibliography in the document, was published in 2001, but the remainder of the reference information matches to the 1997 publication by Leach et al. regarding the "Female Stress Urinary Incontinence Clinical Guidelines Panel Summary Report on Surgical Management of Female Stress Urinary Incontinence." In contrast to the information reported in the marketing piece, this publication shows *more* urethral erosion with synthetic slings, specifically, 2% urethral erosion rate for synthetic materials in contrast to an absence of urethral erosions for homologous materials and 0.3% urethral erosion rate for autologous materials. The marketing piece also notes there were "no reported urethral erosions in 10 clinical studies of 50+ patients." The 10 studies referenced included more than 1,440 patients, similar to the number of patients (1,515) reported in the Leach et al. summary report who were treated with synthetic mesh, but in the Leach et al. article, to which Ethicon cited as discussed above, there were 27 patients (2%) with urethral erosion reported.[409]

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[406] FDCA § 201(n); 21 U.S.C. 321n).
[407] Dr. David Robinson deposition (rough transcript), September 11, 2013, 201:21-25; 202:7-203:14; 204:24-205:21.
[408] ETH.MESH.09746948: License Agreement between Johnson & Johnson International and Medscand Medical A.B.; ETH.MESH.09748308 at ETH.MESH.09748316: Letter Re: Acquisition of Assets related to the Tension free Vaginal Tape (TVT); Laura Angelini deposition, September 16, 2013, 216:6-12; 216:8-15, 272:27-274:5. It is my understanding that Ethicon claims that it is unable to locate evidence of payments to consultants including Pr. Ulmsten and Pr. Nilsson prior to 2003 and, thus, the amount of the payments is likely greater than currently known. Laura Angelini deposition September 16, 2013, 287:21-288:1; 331:23-334:3.
[409] ETH.MESH.00339437 at 438: GYNECARE TVT Marketing Piece titled "5 Years of Proven Performance," 2002.

Further, this marketing piece represents to the physician that there is "no foreign body reaction after PROLENE mesh implantation." The reference given for this statement was a single article in which connective tissue metabolism was evaluated two years after Prolene implantation in 10 women and Mersilene implantation in six women, using the TVT procedure. A minimal inflammatory reaction was found in the Prolene group, while Mersilene resulted in a significant foreign-body reaction two years after implantation.[410] Yet, as discussed previously in this Report, foreign body reaction was expected[411] and, as Dr. Hinoul testified, Ethicon knew "some patients will have more major inflammatory reactions from the foreign body, the mesh, than other patients."[412] Moreover, Dr. Hinoul acknowledged that the foreign body response can cause mesh exposure and mesh erosion.[413] To advise physicians that the TVT mesh has no foreign body reaction based on the described study of 10 patients evaluated only once two years after implantation was disingenuous and misleading.

2. "Only GYNECARE TVT has Long-term Results You Can See…and Believe" Marketing Piece

Similar to the "5 Years of Proven Performance" marketing piece discussed above, the marketing piece titled "Only GYNECARE TVT has Long-term Results You Can See…and Believe" reports that there were "[n]o reported urethral erosions in multiple clinical studies of 50+ patients," citing the same references as cited in the "5 Years of Proven Performance" piece, but this new marketing piece was dated two years later (2004).[414] By contrast, a 2004 review by Bhargava and Chapple of the literature dated 1995 to 2004 on the complications of synthetic suburethral slings, including TVT, reported sling erosion to be one of the most frequently and potentially serious complications with the use of synthetic slings. While the introduction of newer sling materials such as TVT (and SPARC) appeared to have reduced the incidence of erosion, recent studies were noted to report incidences between 0.3% and 4.4%.[415]

This marketing piece also states there is a "[l]ow incidence of serious reported complications, <0.01%" (based on internal data on file).[416] Yet the literature review by Bhargava and Chapple[417] showed de novo urgency reported in 6-15% of patients undergoing TVT and urinary retention rates after TVT ranging generally from 2% to 9%, in addition to the erosion rates cited above and bladder perforation, which was reported as the most frequent intraoperative complication of TVT placement. Abouassaly et al.[418] reported a bladder perforation rate of 5.8% in a review of 241

[410] Falconer C et al. Influence of Different Sling materials on Connective Tissue Metabolism in Stress Urinary Incontinent Women. Int Urogynecol J 2001;Suppl 2:S19-S23.
[411] Dr. Piet Hinoul deposition, June 27, 2013, 565:13-21.
[412] *Id.*, 579:5-11.
[413] *Id.*, 566:1-6.
[414] ETH.MESH.00658058 at 059: GYNECARE TVT Marketing Piece titled "Only GYNECARE TVT Has Long-term Results You Can See…and Believe," 2004.
[415] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.
[416] [416] ETH.MESH.00658058 at 059: GYNECARE TVT Marketing Piece titled "Only GYNECARE TVT Has Long-term Results You Can See…and Believe," 2004.
[417] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.
[418] Abouassaly et al. Complications of tension-free vaginal tape surgery: a multi-institutional review. BJU Int 2004;94:110-113.

patients. The reported rates in the literature vary between 0 and 25%.[419] Ward and Hilton[420] reported a total complication rate of 39% (excluding fever) for tension-free vaginal tape in a comparative trial versus colposuspension as primary treatment for stress incontinence. Among the complications were bladder injury (9%), vaginal perforation (3%), wound infection (2%), retropubic hematoma (2%), vascular injury (1%), tape erosion (1%), and urinary tract infection (in six weeks after surgery, 22%).

In regards to the internal complication rate Ethicon reported as <0.01%, the following response to a communication sent to preceptors is noteworthy. Specifically, preceptors were provided "a copy of the latest complication data for GYNECARE TVT" that was "based on 900,000 patients treated worldwide."[421] Complication rates reported ranged from 0.001% to 0.006%., shown in the final column on the complications chart.[422] Dennis Miller replied: "It's fantastic to know that TVT…[is] still so safe, even with more surgeons participating..I know that all companies make these tables with the same format from the MAUDE database, but all surgeons know that the final column is a farce. Surgeons all over the country discuss it regularly. *Placing a percentage on the chart that is based on an entirely false denominator is quite misleading.*"[423] (Emphasis added.)

It is further noteworthy that in this same marketing piece, the results of the Ward and Hilton study are presented, touting that "[a] multicenter, comparative trial of women with SUI randomized to treatment with GYNECARE TVT or colposuspension found no significant difference in cure rates between the 2 groups." The data presented, however, conflict with the data presented on the prior page of the marketing piece regarding the Nilsson 7-year follow-up of the TVT procedure. The latter, just as presented in the Patient Brochures discussed above, reports a 97% overall success rate.[424] The Ward and Hilton study data presented show a 6-month cure rate of 66% for Gynecare TVT and 57% cure rate for colposuspension, with 2-year cure rates of 63% and 51% for Gynecare TVT and colposuspension, respectively.[425] Finally, this marketing piece also cites often to the Ulmsten/Nilsson studies, but physicians are not informed about the conflict of interest associated with the Ulmsten and Nilsson studies or that such studies used a different device than the TVT, as stated above.

3. "Dependability - GYNECARE TVT™ Family of Products Tension-free Support for Incontinence" Marketing Piece

The marketing piece entitled "Dependability - GYNECARE TVT™ Family of Products Tension-free Support for Incontinence" dated 2010 reports that not a single case of tape erosion, tissue reactions, or other adverse effects of the tape were found in a clinical study at an average of 11.5

[419] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.
[420] Ward K and Hilton P. Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002;325:1-7.
[421] ETH.MESH.00134498: Email series January 13-15, 2006, RE: GYNECARE TVT Latest Complication Data.
[422] No Bates number: Ethicon, Inc. Complaint Reporting Statement – Gynecare TVT* Tension-free Support for Incontinence, based on 900,000 patients treated worldwide. [Note that data cut-off for deaths (10) is reported as November 15, 2005].
[423] ETH.MESH.00134498: Email series January 13-15, 2006, RE: GYNECARE TVT Latest Complication Data.
[424] ETH.MESH.00658058 at 059: GYNECARE TVT Marketing Piece titled "Only GYNECARE TVT Has Long-term Results You Can See…and Believe," 2004.
[425] ETH.MESH.00658058 at 060: *Id.*

years.[426] This is referring to the 11.5 year follow up of the Ulmsten/Nilsson study that was performed with the IVS device by Professor Ulmsten, Professor Nilsson and others. Again, however, this marketing piece does not inform physicians that the device used in the study with 11.5 years of follow up was the IVS, not the actual TVT device and, further, about the substantial conflict of interest that the authors have, as stated more fully above.[427] In addition, the information in the piece does not reveal that only 77% of the original cohort of 90 women were assessed 11.5 years after the TVT operation, and only 59% (53 patients) of the original 90 were available and seen in the clinic for evaluation; the other 16 were assessed outside the clinic by interview.[428] The appropriate, accurate presentation of the data would have been a statement such as the following: "Fifty-three (59%) of 90 patients were available for clinical assessment 11.5 years after TVT surgery and showed no evidence of tape erosion, tissue reactions, or other adverse effects at this time interval post surgery; 16 others interviewed by phone reported no adverse effects. Twenty-one (21) patients were not available for evaluation."

Notably, there were 218 reports of TVT mesh (tape) erosion in the MAUDE database through 2008 (date of 11.5-year study follow-up discussed above), about which Ethicon knew or should have known. Twiss and Raz[429] in this same time period reviewed the literature to summarize rates, etiology, and management of the most common complications encountered with synthetic mid-urethral slings. Postoperative vaginal erosions were noted to be a problem with synthetic slings, with large case series of TVT procedures showing vaginal erosions occurring in 0.2% to 1.8% of cases. Urethral erosions were noted but occurrence rate was not provided. As noted above, a 2004 review by Bhargava and Chapple of the literature dated 1995 to 2004 on the complications of synthetic suburethral slings, including TVT, reported sling erosion to be one of the most frequently and potentially serious complications with the use of synthetic slings. While the introduction of newer sling materials such as TVT (and SPARC) appeared to have reduced the incidence of erosion, studies were noted to report incidences between 0.3% and 4.4%.[430] While the rate of erosions may be low, presentation and management of erosion may be associated with a significant risk of morbidity. For example, Deng et al.[431] presented their experience as a tertiary referral center (UCLA) for major complications of mid-urethral slings. Between June 2001 and August 2005, 26 patients' histories were reviewed and details of the presentation and management of complications were reported. Of the 26 patients, 12 had TVT devices implanted. Findings included mesh in the urethra, bladder, urethra and bladder, or mesh in the urethra with urethrovaginal fistula. Treatment required excision and reconstruction or, in the cases of mesh in the urethra plus urethrovaginal fistula, excision and Martius flap were performed.

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[426] ETH.MESH.02237103: Marketing piece titled "Dependability - GYNECARE TVT™ Family of Products Tension-free Support for Incontinence," 2010.

[427] It should also be noted that in the Nilsson publication of the 11.5 year follow up, Professor Nilsson specifically states that there are no conflicts, when that obviously was not the case. Nilsson et al. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J 2008;19:1043-1047 at 1046

[428] ETH.MESH.00355003 at 003, 005: Nilsson et al. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J 2008;19:1043-1047.

[429] Twiss C and Raz S. Complications of Synthetic mid-Urethral Slings. Issues in Incontinence, Laborie.com, Spring/Summer 2008.

[430] Bhargava S and Chapple CR. Rising awareness of the complications of synthetic slings. Curr Opin Urol 2004;14:317-321.

[431] Deng et al. Presentation and management of major complications of midurethral slings: Are complications under-reported? Neurourology Urodynamics 2007;26:46-52.

Additionally, Deng et al. reviewed both the literature on midurethral slings that included complications in the analysis and also the MAUDE database. These authors noted the discrepancy in reporting of major complications between the literature and the MAUDE database and point out that a true denominator is unknown and, thus, an incidence for major or minor complications cannot be calculated, nor can quantitative comparisons be made between the published literature and the MAUDE database. Moreover, these authors state that practitioners of SUI surgery tend to rely on the published literature as representative data, and therefore may not be aware that sling procedures may be associated with a significant risk of morbidity and mortality, as it may be that the more serious complications tend to be in the MAUDE database.[432] Misleading information such as presented in the marketing pieces discussed herein only further limit the physician's awareness of the potential risks associated with the TVT device.

OPINION #3: TVT System Misbranded as a Result of False or Misleading Labeling

The definition of "false or misleading" is not confined to meaning untrue, fraudulent, or deceptive. Labeling can be deemed by FDA to be misleading and in violation of FDA requirements if it proves deceptive to the customer by creating or leading to a false impression in the mind of the reader. Failure to inform the consumer of facts relevant to statements actually made may cause a "false impression," such that labeling that remains silent concerning certain consequences may be as deceptive as labeling that contains extravagant claims.[433] Labeling that fails to reveal material facts and consequences that may result from product use is considered misleading. Thus, product labeling that fails to include risk information and warnings important to safe use is considered false and misleading.

Ethicon utilized promotional labeling that was false and misleading and failed to reveal material facts. This constituted misbranding. The introduction or delivery for introduction into interstate commerce of any device that is misbranded is a violation of Section 301(a) of the FDCA.[434] Thus, Ethicon deviated from the standard of care required of a medical device manufacturer by the multiple ways in which the TVT device was misbranded, including professional and patient labeling and also promotional labeling that was false and misleading in its representations and/or failed to include known or knowable safety information.

IX. FDA ACTIONS: SERIOUS COMPLICATIONS ASSOCIATED WITH TRANSVAGINAL PLACEMENT OF SURGICAL MESH IN REPAIR OF STRESS URINARY INCONTINENCE

A. 2008 FDA Public Health Notification

By 2008, FDA was aware of potential safety issues with urogynecologic surgical mesh products because of information received through multiple sources. These sources included (1) postmarket

[432] *Id.*
[433] Medical Devices: Labeling Requirements – Misbranding (Available at www.fda.gov).
[434] 21 U.S.C. § 331(a).

surveillance of the MAUDE database for medical device reports (MDRs), (2) concerns raised by the clinical community and citizens, and (3) the published literature.

A search of the MAUDE database in 2008 showed that more than 1000 MDRs had been received from 2005-2007. These were reports of complications from nine surgical mesh manufacturers of surgical mesh devices used to repair pelvic organ prolapse (POP) and stress urinary incontinence (SUI).

As a result of these findings, FDA issued a *Public Health Notification* (PHN) in October 2008 informing clinicians and their patients of these findings, with recommendations on how to mitigate risks and how to counsel patients, titled **"Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence."**[435]

According to the 2008 PHN:

"The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia."

B. 2011 FDA Safety Communication

In January 2011, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2,874 MDRs for urogynecologic surgical mesh; of these, 1,371 were associated with SUI repairs.[436]

On July 13, 2011, FDA issued a *Safety Communication* to update the 2008 PHN.[437] Although directed to health care providers who treat either POP and/or SUI, and patients contemplating or who have received either type of mesh, the Safety Update was primarily concerned with POP repair. However, according to the *Safety Communication*, "[i]n order to better understand the use of surgical mesh for POP and SUI, the FDA conducted a systematic review of the published scientific literature from 1996 – 2011 to evaluate its safety and effectiveness. The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report about that usage at a later date."[438]

[435] FDA *Public Health Notification*: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, Issued October 20, 2008.
[436] FDA *Safety Communication*: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse, Issued July 13, 2011.
[437] *Id.*
[438] *Id.*

C. 2011 Meeting of Obstetrics and Gynecology Devices Advisory Committee and January 4, 2012, Update

In September, 2011, as a result of the above-discussed findings, FDA convened a meeting of the Obstetrics and Gynecology Devices Advisory Committee to discuss "Surgical Mesh For Treatment Of Women With Pelvic Organ Prolapse And Stress Urinary Incontinence." As a background document for this meeting, FDA published an Executive Summary summarizing outcome efficacy and safety data obtained from published literature and the MAUDE safety database.[439] From 1992-2010, the FDA cleared 83 510(k)s for surgical mesh with an SUI indication, 63 with a POP indication, and 22 with both. Meshes were categorized according to whether the indications for use included "reconstruction of the pelvic floor" or "pubourethral support." Premarket clearance of surgical mesh indicated for POP and SUI repair was typically based on pre-clinical bench and animal studies. The FDA premarket notification review process did not request original clinical studies to support 510(k)-clearance. However, in their Executive Summary, FDA states that "A substantial number of quality clinical trials, as well as systematic reviews, have been published for the first generation minimally invasive slings that provide evidence of safety and effectiveness of these devices."[440]

The types of adverse events reported to the FDA's MAUDE database during 2008 to 2010 for surgical meshes to treat SUI were death (n=3), injury (n=1131), malfunction (n=236), and "other" (n=1). Of the three deaths reported, two were related to the mesh placement procedure (two bowel perforations), but unrelated to the mesh itself. One death was related to complications from removal of eroded mesh. Types of non-fatal adverse events are presented in Table IX.1. below.

Table IX.1.: Number and Percent of Adverse Event for SUI Reported to MAUDE (2008-2010)

Adverse Event	# of Reports[1]	Percent[2]
Pain	479	34.9
Erosion	436	31.8
Infection	260	18.9
Urinary Problems	220	16.0
Organ Perforation	110	8.3
Recurrence, Incontinence	103	7.5
Bleeding	103	7.5
Dyspareunia	73	5.3
Neuromuscular Problems	50	3.6
Vaginal Scarring	22	1.6

[1] The total number of reports is greater than the number of MDRs because most MDRs reported more than one adverse event.
[2] Total number of reports divided by 1371 (total number of MDRs received)

[439] FDA Executive Summary. Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting, September 8-9, 2011.
[440] *Id.*

The most frequent required interventions were additional surgical procedure (394), partial or complete mesh removal (162), and hospitalization (58). Other less severe interventions included application of topical estrogen cream, a course of antibiotics or trimming of the exposed mesh.

The FDA also undertook a review of the published literature for safety data associated with SUI slings. They included 187 studies in their review, of which 102 were observational studies and 85 were randomized controlled trials. The most commonly studied procedure using mesh for SUI repair was the TVT procedure, followed by the TOT procedure. Most of the available information was heavily weighted from the perioperative period (intraoperative to 48 hours postoperative) to one year postoperative. Few studies had follow-up longer than three years. The most commonly reported adverse events in the literature associated with surgical mesh for SUI repair included erosion, dyspareunia, infection, pain, urinary problems (including de novo SUI, urgency, frequency and overactive bladder), and re-surgery. Between 9% and 17% of patients who had SUI treated with surgical mesh reported urinary problems from 6 months postoperatively to 60 months postoperatively. It also appeared that with time there were increases in the proportion of women reporting urinary problems, re-surgery (range 2.5% at 6 months postoperatively to 6.2% at 12 months postoperatively), and any infection (5.1% perioperatively to 27.6% at 60 months postoperatively). The trend in urinary problems appeared to be largely driven by TVT procedures, compared to TOT procedures. The latter procedure demonstrated consistent rates (roughly 10%) of urinary problems across study follow-up periods.

The trend observed with urinary problems was similar with infection rates. Women who underwent TOT procedures had lower weighted rates of infection than women who had TVT procedures. Furthermore, it was observed that among TVT and TVT-O procedures, infection rates appeared to increase over time, while infection rates among TOT procedures decreased from 10% during the perioperative period to 0.4% at 24 months postoperatively.

There was no apparent trend in erosion rates, which ranged from 0.25% to 4% from 6 months postoperatively to 60 months postoperatively. Weighted rates of reported pelvic or vaginal pain ranged from 22.2% at 60 months to 1.6% at 36 months but more consistently averaged at about 5%. Neuromuscular adverse events were reported at a rate of 1% or less over the follow-up measurement periods. Dyspareunia rates ranged from a high of 13.7% at 60 months to 0.64% at 12 months.

The most common perioperative complications associated with sling procedures were organ perforation (including bladder, urethral, vaginal, and bowel perforation), hemorrhage, and hematomas. The TVT procedure had a lower rate of perforation (4.4%) than the SPARC procedure (10.1%) or pubovaginal slings (8%), and a higher rate than the TOT procedure (1.7%). Definitions of hemorrhage and hematoma were disparate or absent across the literature; therefore no clinically significant conclusions could be drawn.

Other risks of minimally invasive synthetic slings include perioperative complications such as bladder perforation and groin pain. FDA also concluded that there is potential for serious complications with SUI mesh. They expressed concerned that safety outcomes may not have been comprehensively evaluated by RCTs to date and noted that the safety of SUI repair with mesh needs to be further considered in evaluating the overall risk to benefit profile of these products.

However, they stated that new premarket clinical trials are not warranted for minimally invasive slings for SUI unless the device has new features (e.g., new polymer or coating) that could affect device performance. This is despite the relatively short duration of follow-up (2 years) for most of the studies.

In a January 2012 Update, FDA advised that it continues to assess the safety and effectiveness of urogynecologic surgical mesh devices through a number of sources, including the published literature, epidemiological research on safety and effectiveness of surgical mesh, collaborations with professional societies and other stakeholders to fully understand the postmarket performance of urogynecologic surgical mesh devices and the occurrence of signs and symptoms associated with specific adverse events, and collecting and reviewing all available information about currently marketed urogynecologic surgical mesh devices.[441]

X. POSTMARKET VIGILANCE ISSUES AND MISBRANDING

A. Significance of Postmarket Vigilance

"Postmarket vigilance" means all scientific and data collection activities related to the detection, evaluation, and understanding of adverse events. The primary objective of postmarket vigilance is to identify and evaluate any potential safety signal. The term "signal" refers to a potential safety issue or concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Importantly, in order for an event to be considered a signal, a causal relationship between the device and the event does not need to have been established.

Postmarket vigilance is critical to ensuring that informed and timely decisions are made concerning medical device safety and, thereby, risk to patients is minimized.[442] A manufacturer's postmarket vigilance program can only be effective if all company employees or representatives who learn about complaints, including both adverse events and malfunctions, report them to the individual(s) designated within the company, according to established procedures, for evaluation, investigation, and reporting to FDA as required. Further, those individuals with responsibility for receipt, evaluation, investigation, and reporting of adverse events to FDA, in accordance with applicable requirements (as discussed in Section II.G.), must perform their responsibilities with objectivity, due diligence, and with the ultimate goal of assuring that all safety issues that meet the regulatory reporting requirements are both assessed internally and also submitted to FDA in a timely manner, and that corrective actions are implemented as necessary to protect the public health.

Safety signals can arise from multiple sources: postmarket data for a company's own product, including complaint reports from consumers made directly to the company, reports to FDA that are captured on the FDA's adverse event databases, and information from postmarketing clinical studies; scientific and medical literature; and events associated with other similar products. After a signal is identified, it should be further investigated to determine whether it represents a potential

[441] FDA UPDATE 01/04/2012: Urogynecologic Surgical Mesh Implants.
[442] Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. March 2005, U.S. FDA, CDER/CBER.

safety risk and whether other action should be taken. Such investigation may or may not lead to the conclusion that the device caused the event. FDA advises that a manufacturer should initially evaluate a signal through a careful review of individual case reports and a search for any additional cases. When one or more cases indicate a safety signal that needs further investigation, FDA recommends summarizing the available clinical information in order to characterize the potential safety risk and identify risk factors, if possible.

This section of my Report will discuss Ethicon's actions and inactions according to the MDR regulations and postmarket vigilance activities.

B. Medical Device Reporting/MAUDE Database

As discussed previously in this Report, medical device manufacturers are required to report to the FDA all device-related deaths, serious injuries, and certain malfunctions, in accordance with the Medical Device Reporting (MDR) regulations.[443] Medical Device Reporting provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events in order to detect and correct safety problems in a timely manner. Achieving this purpose is dependent on the compliance and cooperation of the medical device manufacturer to perform its surveillance, investigatory, reporting and follow-up responsibilities, as described above.

MDR reports submitted to FDA are entered into the Manufacturer and User Facility Device Experience (MAUDE) database, which contains reports of adverse events involving medical devices and is accessible via the FDA website. The MAUDE database includes not only MDRs from manufacturers but also MDR reports from user facilities and voluntary reports from such sources as healthcare practitioners, patients, and consumers (e.g., attorneys). The sooner the FDA learns about a problem, the sooner the Agency can take action to evaluate actual or potential risk and ensure that any necessary corrective action is initiated to protect patient safety. Sometimes a single report can initiate this action.[444]

To evaluate the serious adverse event information of particular relevance to the TVT System and known or knowable to Ethicon based on the MAUDE database, an independent search/review of the MAUDE database for Medical Device Reports (MDRs) was undertaken using the methodology described in Exhibit 1. Summary results of that review are presented below. Tabulations providing additional detail and supporting the summary results also are provided in Exhibit 1.

C. Summary of TVT Medical Device Reports

A total of 1,173 Medical Device Reports for the TVT device were located in the MAUDE database (includes 372 TVT reports for which the product catalog number was not available). Of the 1,173 reports, 1,093 were manufacturer reports, 74 were voluntary reports, and six were user facility reports. The reason for surgical implantation of the mesh was not specified for most of the reports (1,018 reports) or stated to be SUI (124 reports) and/or POP (56 reports).

[443] 21 CFR Part 803.

[444] Improving Patient Care by Reporting Problems with Medical Devices. *A MedWatch Continuing Education Article*. Uniformed Services University of the Health Sciences and FDA. September 1997.

It is important to note that, for many patients, more than one adverse event was reported. Also, for this analysis, not every occurrence of a named sign, symptom, or illness was counted; instead, the specific signs, symptoms, and illnesses reported were counted. For example, any number of urinary tract infections (UTIs) described for a particular report was counted only once.

1. Most Commonly Reported Adverse Events

The most commonly reported adverse events, i.e., defined as those occurring in 2% or more of MDR reports, included those listed below in Table X.1. The total number of most commonly reported adverse events and also the percentage of total MDR reports in which such events were reported are shown. Of note, adverse events related to the urinary system are reported collectively as urinary problems in Table X.1. The multiple adverse events represented by "urinary problems" are specified in Section 1.B. of Exhibit 1 and are tabulated by year of report date in Section 2 of Exhibit 1. Similarly, as regards mesh erosion and organ perforation, the organs involved are delineated in Section 1.B. of Exhibit 1 and are tabulated by year of report date in Section 2 of Exhibit 1. As regards the other most commonly reported events, where different reporting terms were used for like events, these were combined as shown in Section 1.B. of Exhibit 1 for the purpose of this analysis and also are tabulated by year of report date in Section 2 of Exhibit 1.

Table X.1. Most Commonly Reported Adverse Events in MAUDE Database: 1999-2010

Event	n	% of total MDRs (1,173)
Urinary Problems	405	34.5%
Erosion	377	32.1%
Pain	291	24.8%
Bleeding	151	12.9%
Sexual Dysfunction	117	10.0%
Organ Perforation	103	8.8%
Infection	82	7.0%
Unspecified Illness/Issues/Injuries	67	5.7%
Discharge	54	4.6%
Wound Healing Problems	45	3.8%
Neurologic Compromise or Damage	35	3.0%
Scarring	34	2.9%

Other adverse events reported are listed in Section 1.B. of Exhibit 1. Patient outcome information reported also is shown in Section 1.B. of Exhibit 1. Some reports do not state a patient outcome.

It is important to note that there were 15 deaths reported associated with TVT implantation. Number of deaths by year reported are indicated following: 1998 (one); 1999 (two); 2000 (one); 2001 (one); 2002 (two); 2003 (three); 2004 (one); 2005 (two); 2008 (one); 2010 (one). Among the causes of death or information available regarding these deaths were the following:

- Bladder mesh, sepsis, and anemia listed on death certificate as cause of death, anterior wall defect;

- During follow-up surgery, patient died when she went into septic shock;
- Patient died in postoperative course from major septic state;
- Expired due to bowel perforation;
- Bowel perforation noted in follow-up surgery, patient died post-op;
- Bowel perforation and abscess noted after surgery;
- Cecal perforation noted after initial surgery and patient developed disseminated intravascular coagulopathy;
- Lost consciousness and expired after surgery;
- Died during initial surgery;
- Patient required resuscitation twice and third resuscitative effort was unsuccessful and patient expired;
- Hematoma evacuated, patient had seizure-like event two days later and died due to pulmonary embolism arising from occult deep vein thrombosis;
- Venous bleeding occurred, vasovagal attack and cardiac arrest.

2. ***Comparison of MDR Reports Located for TVT vs. FDA's MAUDE Search Across SUI Mesh Products of Multiple Manufacturers: 2008-2010***

Table X.2. below shows the number of MDR reports for each adverse event that FDA identified in its Executive Summary of safety data obtained from its search of the MAUDE safety database for the time period 2008 to 2010, which included multiple manufacturers of surgical mesh for the treatment of SUI;[445] also shown are the number of MDR reports identified for TVT for each adverse event in the independent search/review of the MAUDE database for MDR reports using the methodology described in Exhibit 1. Based on this information, for each adverse event, the percentage of events across all manufacturers attributable to TVT is shown.

It is particularly notable that TVT accounts for 82.2% of dyspareunia reports, yet this never appeared in the TVT IFU/professional labeling. Except for organ perforation and infection, for which TVT accounted for 10% and 16.5% of these reported events, respectively, TVT accounted for a third or more of each adverse event identified by FDA as a potential safety concern with the use of surgical mesh to treat stress urinary incontinence. As discussed below in Section X.D., Ethicon underreported some of these adverse events for TVT, e.g., erosions and organ perforation.

[445] FDA Executive Summary. Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence. Obstetrics & Gynecology Devices Advisory Committee Meeting, September 8-9, 2011.

Table X.2. TVT MDRs versus "All" SUI Mesh Product MDRs: 2008-2010

Adverse Event	All Mesh Product Reports[1]		Ethicon TVT Reports		% TVT of All SUI Mesh Reports
	n	%[2]	n	%[3]	
Pain	479	34.9	158	47.3	33
Erosion	436	31.8	195	58.4	44.7
Infection	260	18.9	43	12.9	16.5
Urinary Problems	220	16.0	110	32.9	50.0
Organ Perforation	110	8.3	11	3.3	10.0
Recurrence, Incontinence	103	7.5	40	12.0	38.8
Bleeding	103	7.5	37	11.1	35.9
Dyspareunia	73	5.3	60	18.0	82.2
Neuromuscular Problems	50	3.6	32[4]	9.6	Not applicable[5]
Vaginal Scarring	22	1.6	31[6]	9.3	Not applicable[5]

[1] The total number of reports is greater than the number of MDRs because most MDRs reported more than one adverse event.
[2] Total number of reports divided by 1371 (total number of MDRs received)
[3] Total number of reports divided by 334 (total number of Ethicon TVT reports found through FDA MAUDE database search)
[4] Neuromuscular problem as a specific term was not identified in the TVT MDR reports; the 32 reports shown were for neurologic compromise (26) and nerve damage (6).
[5] Because terms in the TVT MDR reports did not specify location of scarring or further define nerve damage/compromise, a percentage of all mesh product reports is not given.
[6] Includes 29 reports of "scar tissue" and two reports of "scarring"; location of scar tissue/scarring was not specified.

3. Reported Interventions

As regards follow-up surgery, 348 (30.0%) of the MDRs reported that the patient had undergone one follow-up surgery, 177 (15.1%) reported that the patient had undergone two or more follow-up surgeries, and 94 (8.0%) reported that the patient would undergo surgery as a result of the reported adverse events for a total of 619 (52.8%) patients who required surgery or for whom surgery was planned.

Interventions other than surgery and planned surgery are listed in Section 1.D. of Exhibit 1, along with the number of patients for which each intervention type was reported.

4. Initial Reports and Follow-Up Reports

The majority of reports located by the MAUDE DB search were labeled "Initial." While the FDA received most initial reports within 30 days of manufacturer receipt of the report, as required, there were 88 reports with a somewhat longer reporting interval. Sixty-seven (67) reports were reported between 31 and 44 days, six (6) were reported between 45 and 60 days, eight (8) were reported between 61 and 90 days, and seven (7) were reported between 91 and 212 days. A total of 101 reports did not have an entry for "date manufacturer received."

D. TVT Issue Reports, including Investigation Records

An Issue Report is the form Ethicon uses to record complaints, investigation of complaints, and the determination of reportability to regulatory authorities. There were 862 TVT Issue Reports received and reviewed for this Report (date range: 1999-2012). Of these, Ethicon submitted 603 (70%) as MedWatch (MDR) reports to FDA, and 258 (29.9%) were determined by Ethicon to be "not reportable." One was undetermined. Review of the Issue Reports that Ethicon determined to be "not reportable" showed that a number met the requirements for MDR reporting and should have been submitted to FDA in my professional opinion. The basis for this opinion and representative examples are discussed below.

Medical Device Reporting requires that if a manufacturer becomes aware of information that reasonably suggests that its device may have caused or contributed to a serious injury or malfunctioned and the device would be likely to cause or contribute to death or serious injury if the malfunction were to recur, it must report that information to FDA.[446] "Serious injury" includes injury that "results in permanent impairment of a body function or permanent damage to a body structure," or injury that "[n]ecessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure." "Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage."[447] Definitions of other key terms such as "becomes aware," "reasonably suggests," and "caused or contributed" were provided previously in Section II.G.2.1. of this Report. Importantly, a serious injury is not required actually to have occurred for the event to be considered reportable under this definition.[448]

1. MDR-Reportable Adverse Events Determined by Ethicon to be Not Reportable

Provided in Exhibit 3 in tabular format are 29 examples of adverse events that Ethicon determined were not MDR-reportable but should have been reported to FDA as MDRs in my professional opinion. These include 15 reports of erosion/extrusion, five of which resulted in dyspareunia or pain/discomfort to the sexual partner and four of which noted incontinence, including de novo urge incontinence which was specified for one patient and also bladder perforation in one patient. Incontinence was reported in an additional eight (8) reports: incontinence and also hematoma (one report); urge incontinence/urgency and urgency leak (four reports); recurrent SUI (two reports); and worsening of urgency incontinence (one report). There were three additional reports of bladder perforation, one report of blood vessel perforation with hematoma, an additional report of vaginal pain and dyspareunia, and one report of possible TVT allergy.

Of these 29 examples, seven representative complaints involving mesh erosion/extrusion and organ perforation, which are among the adverse events most commonly reported in the MAUDE database for SUI mesh products across multiple manufacturers (based on FDA's search, date range: 2008-2010), are discussed below. In particular, the reasons in my professional opinion that these events were MDR-reportable are presented.

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[446] 21 CFR § 803.20(b)
[447] 21 CFR § 803.3.
[448] Mathewson NW. Complaint Handling and Medical Device Reporting. In *Medical Device Regulation & Compliance*. Eds. Terman SD and O'Flaherty NF. FDLI 2010.

1.1 Mesh Erosions/Extrusions Ethicon Determined Were Not MDR-Reportable

Erosions and extrusions are noted to be potential adverse reactions in the TVT product labeling, i.e., the IFU. As shown above in the discussion of TVT MDR reports, there were 377 MDR reports of mesh erosion, including 151 reports of vaginal mesh erosion and 138 reports of unspecified erosion, during the 1999-2010 time period; of these, 328 total reports of mesh erosion, including 120 reports specified as vaginal erosion, were reported to FDA by Ethicon. It is noteworthy that vaginal erosions requiring a procedure for correction may be treated in the physician's office or in the hospital, but intervention in both cases is considered a surgical revision.[449]

A manufacturer must evaluate each adverse event or malfunction reported and make a good faith determination consistent with the regulations and industry standard of practice, including applying the same logic every time a complaint is evaluated. This is critical for the manufacturer to be able to analyze and trend complaint data to identify any product problem that requires corrective and preventive action. The examples discussed below demonstrate that Ethicon did not consistently submit MDR reports for mesh erosion and, consequently, underreported to FDA the occurrences of mesh erosion following TVT implantation about which it was aware, in violation of the industry standard of care.

a) On January 30, 2002, Ethicon was notified of a patient who presented with minimal asymptomatic vaginal extrusion (Tracking number 30001906).[450] No medical intervention was performed at the time but it was noted that topical estrogen would be used or the mesh would be trimmed if the patient became symptomatic. "The physician felt that the extrusion was probably the result of vaginal atrophy along with passgage [sic] of the needle too close to the vaginal mucosa"; thus the physician noted possible user error. This event was not reported as an MDR on the basis of Ethicon's medical review which concluded that "the patient *will not require* any medical or surgical intervention to correct the extrusion or to otherwise preclude serious injury or permanent damage with regards to the structure or function of the vaginal area." (Emphasis added.) Notably, it was speculation in my professional opinion for the medical reviewer to conclude that the erosion would not worsen and/or require treatment, and I reviewed no evidence of follow up by Ethicon to determine outcome of the erosion. The status was indicated as closed within approximately two months of the alert date.

   As discussed above, a serious injury is not required actually to have occurred for the event to be considered reportable.[451] Additionally, regardless if user error contributed to the occurrence of erosion, the event should be reported if it meets the criteria for MDR reporting. The regulation does not exempt events caused by user error from reporting requirements. In fact, FDA has stated that "reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries."[452] It is significant that approximately 40% of Medical Device Reporting (MDR) filings involve

[449] Dr. Piet Hinoul deposition, June 27, 2013, 487:9-20.
[450] ETH.MESH.02622556-559: Issue Report (Tracking Number: 30001906).
[451] Mathewson NW. Complaint Handling and Medical Device Reporting. In *Medical Device Regulation & Compliance*. Eds. Terman SD and O'Flaherty NF. FDLI 2010.
[452] 60 *Fed. Reg*. 63583.

user error. One of the problem areas is labeling. In addition to the cases where there is a primary association between labeling and MDR reports, labeling can also be an "underlying" or secondary cause of misuse that leads to MDR reports.

Although the rationale given for not reporting this event states that "[t]his event is not indicative of any product malfunction," the device did not perform as intended. FDA indicates that a malfunction is considered reportable if the device is a long-term implant or if a malfunction of the same type has actually caused or contributed to a serious injury in past, both of which apply to the TVT device. Furthermore, if Ethicon considers vaginal atrophy and passage of the needle too close to the vaginal mucosa to be factors that increase the risk of vaginal erosion, then Ethicon had the obligation to include this information in the Warnings and Precautions section of the labeling.

b) Ethicon became aware on August 21, 2002, that a patient approximately six weeks after TVT implantation presented with a loop of the mesh (tape) approximately 3 cm long in the vagina (Tracking number 30002788).[453] Medical intervention to resolve the erosion was to trim the tape. The surgeon attributed the extrusion to an episode of coughing during the postoperative period, and the Ethicon Medical Director agreed. However, the issue report documents that the injury required medical or surgical intervention and that intervention was required to prevent permanent impairment of a body function or permanent damage to a body structure, which by definition makes this an MDR-reportable event. Considering that erosion/extrusion is a labeled adverse reaction, it is not only speculation but also disingenuous to attribute the tape extrusion to coughing. If the Medical Director believed that coughing postoperatively could result in tape extrusion, this information should have been included in the Warnings and Precautions section of the product labeling.

c) On September 20, 2002, an Ethicon Medical Director was contacted by a urologist who reported a 51-year-old woman with vaginal mesh extrusion and dyspareunia two months after TVT implantation (Tracking number 30002949).[454] Medical intervention was reported: cutting of the exposed portion of the tape vaginally. The physician theorized that corticosteroids may have been responsible for thinning of the vaginal wall and tape extrusion. On that basis, Ethicon decided not to report this event as an MDR. Similar to the notation above in paragraphs "a" regarding the report of mesh extrusion as probably related to vaginal atrophy, if Ethicon considers corticosteroid usage to be a risk factor for vaginal extrusion, then the company had the obligation to include this information in the Warnings and Precaution section of the labeling. Notably, the issue report documents that the injury required medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure, which by definition makes this an MDR-reportable event. Disingenuously, the issue report also documented that a person qualified to make a medical judgment concluded that the malfunction would not be the cause or contribute to a death or serious injury if it were to recur. Yet through 2001, Ethicon submitted at least 10 reports of vaginal erosion to FDA as a serious injury, with an additional at least 34 such reports submitted to FDA as MDR reports in 2002. Through 2001, Ethicon submitted nine (9) reports of dyspareunia to FDA as a serious injury, with an

[453] ETH.MESH.02623207-210: Issue Report (Tracking Number: 30002788).
[454] ETH.MESH.02623462-465: Issue Report (Tracking Number: 30002949).

additional 25 such reports submitted to FDA as MDR reports in 2002. By Ethicon's own prior actions, vaginal erosion and dyspareunia are MDR-reportable events.

d) On May 18, 2005, a sales representative reported a customer complaint of multiple adverse events following a vaginal hysterectomy and TVT procedure on May 19, 2004 (Tracking number 30005380).[455] Specifically, since that time, the patient had experienced a series of ongoing post-operative problems: De novo urge incontinence within the first two weeks postoperative, for which Detrol medication was initiated; multiple bladder infections within the past year with no history of bladder infections prior to the procedure; two vaginal tape erosions, both of which required procedures to cut out the tape and, as specified for the second procedure, re-sew the vaginal mucosa on top. Dr. C. Owens reviewed this complaint and provided her assessment that "[u]rge incontinence is sometimes unmasked or a transient known occurrence after TVT placement. When it is transient it is usually self limiting. This is not unique to the TVT device as any sling procedure can have this occur after." It is notable that her discussion is in regard to *transient* urge incontinence, yet this problem had been ongoing for one year when reported. Dr. Owens's further assessment stated that "[m]esh exposure is influenced by many factors including an inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the mesh as this can occur with any permanent implant." As discussed above regarding other events of erosion or extrusion that were not submitted as MDR reports, if Ethicon considered inadequately estrogenized vaginal mucosa, trauma, and improper closure to be risk factors for erosion, the company had the obligation to include these in the Warnings and Precautions section of the labeling. Finally, the rationale provided for not reporting this complaint was "that there was no device malfunction or serious injury [that] occurred. Persistent urinary stress incontinence following a sling procedure with TVT is likely the result of sub optimal placement of the device and is not likely due to the failure of the device itself. The patient would have the same clinical presentation as before the procedure and this condition is not considered life threatening or serious to the patient." It is noteworthy that this rationale focuses on SUI, yet Dr. Owens specifically commented that the patient's ongoing incontinence is not SUI according to the urodynamics noted in the complaint. Further, the rationale ignores that the device failed to perform as intended, notably, that the patient had two erosions that required medical or surgical intervention; additionally, the patient experienced multiple bladder infections. It is disingenuous to conclude that no serious injury occurred, when by end 2004, Ethicon, to the contrary, had reported at least 80 cases of vaginal erosion to FDA as serious injuries and an additional 57 cases of unspecified erosion or erosion into other organs, for a total of 137 reports of mesh erosion submitted to FDA as serious injuries. Moreover, Ethicon had reported 40 complaints of incontinence to FDA as serious injuries and 20 complaints of urinary tract infections to FDA as serious injuries by end 2004. As regards the speculation that persistent SUI is likely the result of sub-optimal placement of the TVT, even if this were true, the regulation does not exempt events caused by user error from reporting requirements, as previously discussed.

e) On June 20, 2005, Ethicon received a report of a gynecologist stating that s/he has had four or five erosions since the tape was changed to blue, yet had no erosions previously with the

[455] ETH.MESH.02627651-655: Issue Report (Tracking Number: 30005380).

undyed tape during an 18-month period (Tracking number 30005489).[456] Physician stated belief that the dying procedure had affected the property of the tape, as it is less soft, pliable and flexible. Medical Director Dr. C. Owens provided the medical opinion that the blue pigment would not alter the physical characteristics and be responsible for the mesh exposures, but exposures are influenced by such factors as "inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the mesh as this can occur with any permanent implant." Further rationale for not reporting these events was "that neither serious [injury] nor device malfunction which could lead to a serious injury have occurred. Event reported is a customer preference issue. It does not affect the efficacy of the product or present a risk for serious injury to the patient." As discussed above regarding other events of erosion or extrusion that were not submitted as MDR reports, if Ethicon considered inadequately estrogenized vaginal mucosa, trauma, and improper closure to be risk factors for erosion, the company had the obligation to include these in the Warnings and Precautions section of the labeling. Further, as also discussed above, it is disingenuous to conclude that neither serious injury nor malfunction that could lead to serious injury had occurred, when by end 2004, Ethicon had reported at least 80 cases of vaginal erosion to FDA as serious injuries and an additional 57 cases of unspecified erosion or erosion into other organs, for a total of 137 reports of mesh erosion submitted to FDA as serious injuries. Significantly, I found no evidence to indicate that any effort was made to investigate the multiple cases of erosion reported in this complaint in order to learn and report, as necessary, patient outcomes.

1.2 Organ Perforations Ethicon Determined Were Not MDR-Reportable

Punctures or lacerations of vessels, nerves, bladder or bowel during needle passage, possibly requiring surgical repair, are noted to be potential adverse reactions in the TVT product labeling. As shown above in Table X.1., there were 103 MDR reports of organ perforation submitted during the 1999-2010 time period, of which 98 were submitted by Ethicon. The examples below of complaints involving organ perforation demonstrate that Ethicon was inconsistent in its determination of MDR-reportability of such events and that Ethicon underreported to FDA occurrences of organ perforation following TVT implantation, just as it underreported mesh erosion and extrusion, in violation of the industry standard of care.

a) Ethicon received a call on September 24, 2004, from a sales representative with a physician complaint regarding TVT. Ethicon WCQ appropriately followed up to obtain more information and learned that the surgeon had performed a TVT procedure on August 10, 2004, and inadvertently punctured the patient's bladder during the procedure (Tracking number 30004870).[457] The first device was removed and a second one was placed. Two days later the patient complained of urinary retention and was managed with Ditropan. A cystoscope was performed (apparently on September 30, 2004) and revealed a vaginal mesh erosion and "something pressing on the bladder," which was causing frequency and incontinence. It was also reported that the cystoscope identified fragments of mesh in the bladder from the original inadvertent bladder perforation.

[456] ETH.MESH.02627743-747: Issue Report (Tracking Number: 30005489).
[457] ETH.MESH.02627146-150: Issue Report (Tracking Number: 30004870).

Ethicon Medical Director Dr. Owens reviewed the complaint and followed up appropriately to obtain more information. In addition to the above information, Dr. Owens learned that the patient required a Foley catheter for several days and continued to have some urinary retention after removal of the Foley catheter, such that she had to move her body into certain positions in order to void. Shortly after catheter removal, she developed urge and frequency and a cystoscopy was performed by a urologist, who observed "pieces of the TVT in the bladder and a suburethral erosion in the vaginal mucosa with a finger like 'something', maybe a hematoma, compressing down on the left side of the bladder." Removal of the TVT device was planned within approximately one week. Patient had urgency and incontinence. Dr. Owens noted that the individual with whom she spoke (name redacted) felt the pieces in the bladder were not erosions but were left behind when she removed the TVT device after perforating the bladder. Further, Dr. Owens noted that the "bladder entry was technique-related and also related to the fact that the patient had a history of previous surgery which may have also contributed. The vaginal erosion of TVT tape may be the result of many factors including an inadequately estrogenized vaginal mucosa, trauma, improper closure and other things, but not the direct fault of the device as this can occur with any permanent implant."

Rationale for not reporting stated that "no serious injury or device malfunction occurred in this event. No medical intervention was provided for the bladder perforation and per the Medical Director the etiology of the bladder entry was technique related and also related to the fact that the patient had a history of previous surgery that may have also contributed."

Similar to the above discussions regarding examples of mesh erosion or extrusion that were not reported as MDRs but should have been in my professional opinion, it is disingenuous to conclude this patient had no serious injury or device malfunction and no medical intervention. To the contrary, the device did not perform as intended. The device eroded into the vagina and the patient was incontinent with urgency after the TVT implantation. The patient received medication to manage urinary retention postoperatively and subsequently underwent cystoscopy. A possible hematoma was observed. Surgery to remove the mesh was planned in the near term, yet I found no evidence of follow-up to determine outcome post removal of the device or to determine if there were any deleterious effects of the mesh pieces remaining in the bladder. Instead, this complaint was closed out within 18 days after Ethicon became aware of this complaint. As regards the Medical Director's conclusion that the bladder perforation was technique-related, user error does not justify the failure to report this event. Specifically, the regulation does not exempt events caused by user error from reporting requirements. As noted previously, FDA has stated that "reports of adverse events that result from user error may alert FDA to the need for improved labeling to prevent future injuries."[458] Further, if Ethicon considers that a patient's prior surgical history elevates the risk for bladder perforation, then Ethicon had the obligation to include this information in the Warnings and Precaution section of the labeling.

b) Ethicon Medical Director became aware on March 24, 2005, of a TVT procedure on that day in which cystoscopy showed mesh in the bladder, at which point the decision was made

[458] 60 *Fed. Reg*. 63583.

to cut and withdraw the mesh (Tracking number 30005250).[459] Another device was provided and cystoscopy equipment was replaced. Repeat cystoscopy showed no mesh in the bladder. Patient was discharged and returned with complaints of dark urine postoperatively and serosanquineous leakage with foley catheter in place. A second surgery was performed the day after the initial procedure and the bladder showed two perforations from the surgery the prior day and a "button hole" in the vagina, with mesh buried underneath the mucosa. The button hole was repaired during the second procedure. The complaint report states that "[i]t does not appear that the device malfunctioned. The bladder perforation and the vaginal 'button hole' would not be due to the direct fault of the device rather it would be due to surgical technique." This conclusion was affirmed by the Medical Director, Dr. C. Owens. Rationale for not reporting this event included "that the reported injury is readily apparent to the clinician, at which point the clinician may either continue with this device, with another device or treatment modality, or completely abort the procedure." Notably, each of these proposed options as to how the clinician could have addressed this event presented potential additional risk to the patient, e.g., impact on safety and effectiveness, extended duration of surgery and thus anesthesia, or re-operation.

As discussed previously, the regulation does not exempt events caused by user error from reporting requirements if an event meets the criteria for MDR reporting. The patient was exposed to extended surgical time and additional risk as a result of removal of the initially-placed implant and placement of a second device. It is notable that the complaint record states that based on "information from the Medical Director the MDR will be reset to reflect that no medical/surgical intervention was needed or performed for the bladder perforation." To the contrary, the "patient was taken to the OR" due to the postoperative complaints and, while the two holes in the bladder were identified and the injury was expected to heal on its own, the "button holed" area of the vagina was repaired. It is important to recall that the TVT system includes not only the polypropylene tape with polyethylene sheath, both of which are attached to two stainless steel needles, but also a stainless steel introducer and rigid catheter guide. As Dr. Axel Arnaud confirmed, "the TVT is essentially a surgical procedure rather than a product," stating that "[m]ost of it is in the surgical approach."[460] Accordingly, user error in the surgical technique is not a basis for determining an event is not MDR-reportable. User error may be the sole cause or only contribute to an MDR-reportable event. MDR reports of adverse events that result from user error are important, because they can serve to alert FDA that improved labeling and/or training may be needed to prevent future injuries. Device injuries resulting from user error may show that the device is misbranded in that it does not have adequate directions for use or adequate warnings.[461]

2. Malfunctions Ethicon Determined Were Not MDR-Reportable

Medical Device Reporting requires that a manufacturer report a malfunction to FDA if the device or a similar device it markets would be likely to cause or contribute to a death or serious injury if the

[459] ETH.MESH.02627532-536: Issue Report (Tracking Number: 30005250).
[460] Dr. Axel Arnaud deposition, July 19, 2013, 138:12-16.
[461] Medical Device Reporting for Manufacturers, Department of Health and Human Services, Public Health Service, Food and Drug Administration, March 1997.

malfunction were to recur.[462] The regulation assumes that a malfunction will recur.[463] FDA has determined that a malfunction is reportable if it meets any one of several criteria, the following of which are applicable to the TVT:

- it causes the device to fail to perform its essential function and compromises the device's therapeutic effectiveness which could cause or contribute to a death or serious injury;[464,465]
- the device involves a long-term implant[466] or involves an implant malfunction that would be likely to cause or contribute to death or serious injury.[467]

"Malfunctions of long-term implants are not routinely or 'automatically' reportable unless the malfunction is likely to cause or contribute to a death or serious injury if it recurs."[468]

Exhibit 4 provides examples of malfunctions that were MDR-reportable in my professional opinion but for which Ethicon did not submit MDR reports to FDA. Specifically, Exhibit 4 provides descriptions of 10 such reports, including the following:

- Eight (8) reports of the mesh fraying or unraveling and/or fragments falling off or the tape becoming particles;[469,470,471,472,473,474,475,476]
- One report of "[a]bout 2mm foreign matter like stone [that] was found at vaginal mucous membrane," suspected by surgeon to be portion of the product that frayed, moved into the vaginal cavity, "became nucleus of the foreign matter and formed a foreign matter like a stone";[477]
- One (1) report of a problem that occurred in three patients, notably, that "the overlap on the sheath came apart exposing the tape and therefore making it difficult to place the tape in the correct position without causing any further trauma to the patient" and in one case having to hold the sheath together, causing concern of possible damage to the tape

[462] 21 CFR § 803.50(a).
[463] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.
[464] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.
[465] Medical Device Reporting for Manufacturers, Department of Health and Human Services, Public Health Service, Food and Drug Administration, March 1997.
[466] Medical Device Reporting: An Overview, April 1996, Prepared by Office of Surveillance and Biometrics Systems Division of Surveillance, CDRH, FDA.
[467] Medical Device Reporting for Manufacturers, Department of Health and Human Services, Public Health Service, Food and Drug Administration, March 1997.
[468] FDA Compliance Program Guidance Manual 7382.845, Attachment C.
[469] ETH.MESH.02627350-354: Issue Report (Tracking Number: 30005087).
[470] ETH.MESH.02627669-673: Issue Report (Tracking Number: 30005383).
[471] ETH.MESH.02627517-521: Issue Report (Tracking Number: 30005210).
[472] ETH.MESH.02627780-784: Issue Report (Tracking Number: 30005522).
[473] ETH.MESH.02627494-498: Issue Report (Tracking Number: 30005193).
[474] ETH.MESH.02628220-225: Issue Report (Tracking Number: 10100026906).
[475] ETH.MESH.02628155-160: Issue Report (Tracking Number: 10100023117).
[476] ETH.MESH.02630272-277: Issue Report (Tracking Number: 10100114785).
[477] ETH.MESH.02630120-126: Issue Report (Tracking Number: 10100108279).

(noted in complaint that TVT devices used had "sheath shortened from the 5cm overlap to the 2cm overlap" and that surgery was extended 15 minutes).[478]

In one report of small fragments of Prolene falling off when the mesh was lightly touched, cut, or stretched, it was noted that the surgery was extended 10 minutes. Moreover, this customer was concerned that the mesh fragments would "reject in the body and/or create infections and erosions" and also "about fragments traveling in the body."[479] Thus, it is noteworthy that the "foreign matter like stone" complaint described above was believed by the surgeon to have resulted from a mesh fragment having eroded into the vaginal cavity. This "foreign matter like stone" was observed seven to eight years after TVT implantation.[480] In another report of "tape becoming particles," it was stated that the surgeon notified the patient that "intensive postoperative surveillance" was needed; customer also stated "[t]here is a high probability that this device will not act as intended for the treatment of stress urinary incontinence due to its lake [sic] of mechanical strength. It's the first use of the Blue TVT."[481]

Ethicon's rationale for not reporting these malfunctions as MDRs typically included one or both of the following reasons:

- "Not a reportable event in that the reported malfunction is readily apparent to the clinician, at which point the clinician may either continue with another device or treatment modality or completely abort the procedure."
- "There is no evidence to suggest that the device itself caused any permanent impairment or damage to body function or body structure."

In one case, the given rationale included that the event was not reportable because it "*occurred post-procedure* and no actual device malfuntion [sic] is cited,"[482] yet the tape unraveled and became particles; after implantation, the staff remarked there were remaining particles in the box.[483] [Emphasis added.] For another complaint, the rationale for not reporting the event as an MDR included that it "does not indicate that a serious injury occurred, or that medical intervention was required to prevent a serious injury."[484] In the latter case, the "tape frayed from [the] edges," had "less memory and [stayed] stretched during tensioning. Additionally, it was noted that "[b]its of frayed ends may have lodged inside the patient."[485] As discussed previously in this Report, concerning a complaint about "uneven/inconsistent tape width as well as fraying edges," Medical Director Dr. Martin Weisberg stated, "…I don't think we have any idea whether the tape inconsistencies are clinically significant or not…"[486] Thus, it could not be ruled out that this malfunction might compromise the therapeutic effectiveness of the TVT and cause or contribute to a serious injury and, therefore, was MDR-reportable.

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[478] ETH.MESH.02627775-779: Issue Report (Tracking Number: 30005511).
[479] ETH.MESH.02627350-354: Issue Report (Tracking Number: 30005087).
[480] ETH.MESH.02630120-126: Issue Report (Tracking Number: 10100108279).
[481] ETH.MESH.02627517-521: Issue Report (Tracking Number: 30005210).
[482] ETH.MESH.02627669-673: Issue Report (Tracking Number: 30005383).
[483] *Id.*
[484] ETH.MESH.02628220-225: Issue Report (Tracking Number: 10100026906).
[485] *Id.*
[486] ETH.MESH.03905472 at 473-474: Email series April 23-June 6, 2001, initiated by Richard Hu, Johnson & Johnson Medical Taiwan, Re: TVT recommendation from Dr. Alex Wang.

The stated rationales for not reporting the events in Exhibit 4 as MDRs are inconsistent with the FDA-established criteria for MDR reporting of malfunctions described above. Specifically, TVT product labeling (i.e., the IFU) does not caution the TVT user that the mesh may fray and become particles. Further, there is no mention in the product description or instructions for use that mesh fraying or particle loss is normal. Although it was sometimes noted in the event description that there was no adverse patient outcome, these events were product malfunctions and can reasonably be considered to compromise the device's therapeutic effectiveness, which has the potential to necessitate re-operation to remove the device and treat recurrent SUI. One surgeon pointed out (noted above) that "[t]here is a high probability that this device will not act as intended for the treatment of stress urinary incontinence…"[487] Also, it cannot be ruled out that the mesh fragments may cause or contribute to a serious injury longer-term. For these reasons, Ethicon had an obligation to report these malfunctions to FDA in my professional opinion.

A reasonably prudent medical device manufacturer also would have performed due diligence to follow up these events to determine if there were any longer-term sequelae. I found no evidence that Ethicon performed any such actions, and all complaints were closed within less than one month to less than four months, unless reopened due to receipt of complaint sample (one case).[488] Notably, in disregard of the response to a complaint provided by an Ethicon "rep," specifically, that "[u]ntil patient is followed up in a few months time, we won't know if there are any adverse effects ie. Failed procedure at 3 month follow up," the complaint was closed in less than two months from the alert date.[489] FDA requires a manufacturer to make a good faith effort to obtain information about a complaint; the focus of follow-up investigations should be on obtaining information, not on the number of attempts.[490] By its failure to perform meaningful due diligence in following up these complaints to obtain supplemental information on their longer-term outcome, Ethicon violated the standard of care required of a medical device manufacturer.

As regards the complaint of the sheath coming apart and exposing mesh (described above), in which multiple concerns were noted, i.e., about difficulty in placing the tape correctly, further trauma to the patient, and damage to the tape, it is notable that the IFU specifically advises that "[p]remature removal of the sheath may make subsequent adjustments difficult."[491] This complaint represented a product malfunction and reasonably could be considered to compromise the device's therapeutic effectiveness, with the potential to necessitate subsequent medical or surgical intervention.

In summary, Ethicon's determination that the malfunctions included in Exhibit 4 and discussed above were not MDR-reportable was faulty. There was no basis on which Ethicon could reasonably conclude that recurrence of these problems would not be likely to result in serious injury or that the malfunctions did not cause the device to fail to perform its essential function and compromise its therapeutic effectiveness, which could cause or contribute to a serious injury. Based on my synthesis and analysis of the information discussed above and my knowledge, training, and

[487] ETH.MESH.02627517-521: Issue Report (Tracking Number: 30005210).
[488] ETH.MESH.02627669 at 670: Issue Report (Tracking Number: 30005383).
[489] ETH.MESH.02630272: Issue Report (Tracking Number: 10100114785).
[490] Medical Device Reporting for Manufacturers, CDRH, FDA, March 1997.
[491] ETH.MESH.02340471 at 484: Gynecare TVT™ IFU, 10/04.

experience in medical product development and adverse event reporting, a reasonably prudent medical device manufacturer would have reported these events as MDRs and proactively followed up longer-term to assess whether there were any sequelae potentially associated with the discussed TVT malfunctions.

E. FDA Inspection 08/29/2005 – 09/08/2005: Form FDA 483 and Establishment Inspection Report (EIR)

FDA conducted an inspection of Ethicon during August to September 2005 "to follow up on multiple Medical Device Reports (MDRs) involving death and serious injury events."[492] "On 9/8/05, a FDA-483 (Inspectional Observations) was issued to and discussed with Ms. Catherine V. Beath, Worldwide Vice President Quality and Compliance." Significantly, "[t]he inspection revealed an objectionable condition concerning that investigation of MDR reportable complaints did not include a determination of whether the device failed to meet specifications. Investigations conducted for multiple MDR events related to the firm's TVT (Tension Free Vaginal Tape) Device, TVT Obturator, and Thermachoice II Balloon Catheter did not show a determination of whether the device failed to meet specifications. In addition, the records of complaint investigations do not include the determination of the need for corrective and preventive actions."[493]

OPINION #4: TVT System Misbranded Due to Failure to Meet the Postmarket Vigilance Standard of Care and Manage Risk

MDR reporting helps to ascertain the safety profile of the device postmarketing in order to ensure it is safe and effective for its intended use or to initiate timely corrective action if safety or effectiveness concerns arise. Accordingly, as advised in the GHTF guidance titled, "Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative," "[a]s a general principle, there should be a pre-disposition to report rather than not to report in case of doubt on the reportability of an event."[494]

Objective due diligence must be applied to the evaluation of complaint reports in order to manage potentially evolving risks. I reviewed a number of medical reviews of TVT complaints that demonstrated an apparent lack of knowledge and/or understanding of MDR reporting requirements in my professional opinion. To that point, Medical Director Dr. Martin Weisberg testified as follows in response to questions regarding the criteria that qualify an event as reportable to FDA: "That would have to come from our quality department. I don't know what the FDA's rules are."[495] That is an extraordinary admission from a Medical Director who has the responsibility for reviewing events and making determinations that result in MDR-reporting decisions. The contribution of the TVT System as a potential factor in a number of complaints was minimized or negated; for example, events were assessed as technique- or user-related, as due to other

[492] ETH.MESH 07281435 at 437: Ethicon, Inc., Establishment Inspection Report, 08/29/2005 – 09/08/2005.
[493] ETH.MESH 07281435 at 437: Ethicon, Inc., Establishment Inspection Report, 08/29/2005 – 09/08/2005.
[494] GHTF FINAL DOCUMENT: Adverse Event Reporting Guidance for the Medical Device Manufacturer or its Authorized Representative, June 29, 1999.
[495] Dr. Martin Weisberg deposition, August 9, 2013, 954:5-955:21.

speculative causes (e.g., erosion due to vaginal atrophy, corticosteroids, etc.), and decision was made there was no device malfunction or injury to the patient in such case as vaginal extrusion of the mesh that bothered the patient and required trimming. Ethicon failed to implement consistently effective and objective due diligence. As a result, MDR reports for MDR-reportable events were not submitted to FDA as required by 21 CFR Part 803, Subpart E.

Most of the MDR reports reviewed were initial reports, with approximately 15% comprising follow-up reports. Ethicon had the responsibility to follow up reported events until resolution or no further information was available as determined through good faith due diligence. In my professional opinion, Ethicon deviated from the standard of care required of a medical device manufacturer by its failures to follow up reports of unresolved adverse events.

By its failure to report MDR-reportable events to FDA, such as those that have been discussed above, Ethicon denied FDA of the knowledge of these events and also physician users and patients of this clinically important information, which has import for product decisions and patient management. FDA depends on the compliance of the manufacturer with MDR reporting requirements for the Agency to be able to perform its role in postmarket surveillance and identifying any potential safety signal(s) that may require corrective action.

As pointed out by then CDRH Director, Office of Compliance, Timothy Ulatowski, MDR reports and complaints are among the principal methods used to assimilate product information and take action as needed.[496] In my professional opinion, Ethicon deviated from the standard of care by its failure to report to FDA a number of adverse events and malfunctions that met the criteria for Medical Device Reporting, rendering the TVT devices misbranded as a result of failure to furnish information requested under Section 519 of the FDCA.[497] The FDA depends on the manufacturer's cooperation and compliance with the Medical Device Reporting regulations to protect the public health.

XI. SUMMATION OF OPINIONS: STANDARD OF CARE AND DEVIATIONS

The FDCA prohibits the introduction into interstate commerce of misbranded devices [FDCA § 301 (a)] and sets forth the circumstances in which a device would be misbranded (FDCA § 502). Ethicon deviated from the required standard of care by misbranding the TVT devices in multiple ways and otherwise violated the standard of care expected of a reasonably prudent medical device manufacturer as specified in my professional opinions below, each of which has been discussed previously in this Report but is summarized here for ease of reference.

OPINION #1: Failure to Conduct Appropriate Testing

The information discussed in this Report concerning the potential for persistent foreign body reaction and chronic inflammation, mesh degradation, cytotoxicity, chronic infection leading to chronic inflammation, and the potential for carcinogenicity highlight numerous potential concerns of TVT mesh implantation about which Ethicon not only failed to warn healthcare practitioners and

[496] Ulatowski TA. Risk Management: A Regulatory Perspective, Presentation, Beijing, October 2008.
[497] FDCA § 502(t).

patients but also failed to investigate through appropriate testing. Summarily, Ethicon failed to perform testing that was critical to learning the long-term safety of the TVT permanent implant and thus fell below the standard of care required of a reasonably prudent medical device manufacturer. Moreover, Ethicon failed to comply with its own credo, specifically, that the company's first responsibility is to the doctors and patients who use Ethicon's products."[498]

OPINION #2: TVT System Misbranded Due to Failure to Warn

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively. Required use information includes indications, effects, routes, methods, and any relevant hazards, contraindications, side effects, and precautions under which the device can be used safely.[499] Labeling that fails to reveal material facts and consequences that may result from product use is considered misleading. Thus, product labeling that fails to include risk information, warnings, and directions important to safe use is considered false and misleading.

TVT devices were misbranded as a result of Ethicon's failure to warn both healthcare providers/physicians and also patients about multiple potential risks known or knowable to Ethicon from the time of product launch. The company knew or should have known of multiple risks associated with the TVT System that were not included in the Instructions for Use (IFU) and patient labeling information. Nor did the patient labeling show fair balance of benefit vs. risk information. Labeling that is false or misleading and does not bear adequate directions for use, including adequate warnings, causes a device to be misbranded.[500,501] In my professional opinion, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing a product that was misbranded because of the stated labeling deficiencies. Further, by its failure to take appropriate actions through labeling to manage risk associated with its product, Ethicon fell below the standard of care for a reasonably prudent medical device manufacturer.

OPINION #3: TVT System Misbranded as a Result of False or Misleading Labeling

The definition of "false or misleading" is not confined to meaning untrue, fraudulent, or deceptive. Labeling can be deemed by FDA to be misleading and in violation of FDA requirements if it proves deceptive to the customer by creating or leading to a false impression in the mind of the reader. Failure to inform the consumer of facts relevant to statements actually made may cause a "false impression," such that labeling that remains silent concerning certain consequences may be as deceptive as labeling that contains extravagant claims.[502]

Ethicon utilized promotional labeling that was false and misleading and failed to reveal material facts. This constituted misbranding. The introduction or delivery for introduction into interstate commerce of any device that is misbranded is a violation of Section 301(a) of the FDCA.[503]

[498] Exhibit T-115 (no Bates number): Johnson & Johnson credo.
[499] 21 CFR § 801.109(d).
[500] FDCA § 502(a), 21 U.S.C. § 352(a).
[501] FDCA § 502(f)(2).
[502] Medical Devices: Labeling Requirements – Misbranding (Available at www.fda.gov).
[503] 21 U.S.C. § 331(a).

Thus, Ethicon deviated from the standard of care required of a medical device manufacturer by the multiple ways in which the TVT device was misbranded, including professional and patient labeling and also promotional labeling that was false and misleading in its representations and/or failed to include known or knowable safety information.

OPINION #4: TVT System Misbranded Due to Failure to Meet the Postmarket Vigilance Standard of Care and Manage Risk

Ethicon failed to implement consistently effective and objective due diligence in the evaluation of complaint reports in order to manage potentially evolving risks, minimizing or negating the contribution of the TVT device as a potential factor in a number of adverse event reports. Thus, MDR reports for MDR-reportable events were not submitted to FDA as required by 21 CFR Part 803, Subpart E. Ethicon also failed to follow up to learn the outcome of adverse events unresolved at the time of reporting or at the time determined not to be MDR-reportable. In my professional opinion, Ethicon deviated from the standard of care by its failure to report to FDA a number of adverse events that met the criteria for Medical Device Reporting, rendering the TVT devices misbranded as a result of failure to furnish information requested under Section 519 of the FDCA.[504] The FDA depends on the manufacturer's cooperation and compliance with the Medical Device Reporting regulations to protect the public health.

XII. CONCLUSIONS

Based on my professional experience, knowledge, and training and my review, evaluation, integration, and synthesis of the information identified and discussed in this Report, including the materials and scientific/medical literature specified in Appendices B and C and information presented in Exhibits 1 through 4, it is my professional opinion, to a reasonable degree of scientific and professional probability, that Ethicon violated those duties required of a reasonably prudent medical device manufacturer.

The TVT System devices were misbranded due to multiple labeling issues, including false and misleading information, inadequate directions for use, specifically, inadequate warnings and information about potential risks. The devices were misbranded due to a failure to reveal material facts as to the consequences that might result from the use of the device. Additionally, the TVT devices were misbranded because of Ethicon's failure to submit MDR reports for a number of adverse events that qualified for reporting under Section 519 of the FDCA.

[504] FDCA § 502(t).

As a consequence of these multiple failures, Ethicon marketed a product that violated safety and ethical standards and, notably, the Johnson & Johnson credo, which begins as follows: "We believe our first responsibility is to the doctors, nurses and patients, to mothers and fathers and all others who use our products and services. In meeting their needs everything we do must be of high quality."[1] Both the physicians using the TVT System devices and the patients in whom these devices were used lacked the necessary information to make an informed decision about the risks versus the benefit of using this device instead of an alternative method of treatment. Accordingly, the standard of care for the protection of the rights, safety, and welfare of patients was violated, thus disrupting the regulatory process and the protections that exist specifically to safeguard the public health.

I reserve the right to amend or supplement this Report in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

Peggy Pence, PhD, RAC, FRAPS

October 14, 2013

Date

[1] Exhibit T-115 (no Bates number): Johnson & Johnson credo.